

mRNA encoded by LOC169611, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169611 BINDING SITE, designated SEQ ID:40285, to the nucleotide sequence of VGAM340 RNA, herein designated VGAM RNA, also designated SEQ ID:3051.

[17712] Another function of VGAM340 is therefore inhibition of LOC169611 (Accession XM\_095809). Accordingly, utilities of VGAM340 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC169611. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 341 (VGAM341) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17713] VGAM341 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM341 was detected is described hereinabove with reference to Figs. 1–8.

[17714] VGAM341 gene, herein designated VGAM GENE, is a viral



gene contained in the genome of Tobacco Mosaic Virus. VGAM341 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[17715] VGAM341 gene encodes a VGAM341 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM341 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM341 precursor RNA is designated SEQ ID:327, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:327 is located at position 2648 relative to the genome of Tobacco Mosaic Virus.

[17716] VGAM341 precursor RNA folds onto itself, forming VGAM341 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17717] An enzyme complex designated DICER COMPLEX, `dices` the VGAM341 folded precursor RNA into VGAM341 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM341 RNA is designated SEQ ID:3052, and is provided hereinbelow with reference to the sequence listing part.

[17718] VGAM341 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM341 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM341 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17719] VGAM341 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM341 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM341 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM341 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM341 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17720] The complementary binding of VGAM341 RNA, herein designated VGAM RNA, to host target binding sites on VGAM341 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM341 host tar-

get RNA into VGAM341 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17721] It is appreciated that VGAM341 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM341 host target genes. The mRNA of each one of this plurality of VGAM341 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM341 RNA, herein designated VGAM RNA, and which when bound by VGAM341 RNA causes inhibition of translation of respective one or more VGAM341 host target proteins.

[17722] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM341 gene, herein designated VGAM GENE, on one or more VGAM341 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17723] It is yet further appreciated that a function of VGAM341 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of viral infection by Tobacco Mosaic Virus. Specific functions, and accordingly utilities, of VGAM341 correlate with, and may be deduced from, the identity of the host target genes which VGAM341 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[17724] Nucleotide sequences of the VGAM341 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM341 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM341 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM341 are further

described hereinbelow with reference to Table 1.

[17725] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM341 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM341 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17726] As mentioned hereinabove with reference to Fig. 1, a function of VGAM341 gene, herein designated VGAM is inhibition of expression of VGAM341 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM341 correlate with, and may be deduced from, the identity of the target genes which VGAM341 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17727] GRB2-associated Binding Protein 2 (GAB2, Accession NM\_012296) is a VGAM341 host target gene. GAB2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GAB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAB2

BINDING SITE, designated SEQ ID:14649, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17728] A function of VGAM341 is therefore inhibition of GRB2-associated Binding Protein 2 (GAB2, Accession NM\_012296), a gene which act as adapters for transmitting various signals. Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAB2. The function of GAB2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM53. Growth Hormone Receptor (GHR, Accession NM\_000163) is another VGAM341 host target gene. GHR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GHR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GHR BINDING SITE, designated SEQ ID:5674, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17729] Another function of VGAM341 is therefore inhibition of

Growth Hormone Receptor (GHR, Accession NM\_000163). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GHR. Gap Junction Protein, Alpha 1, 43kDa (connexin 43) (GJA1, Accession NM\_000165) is another VGAM341 host target gene. GJA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GJA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GJA1 BINDING SITE, designated SEQ ID:5681, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17730] Another function of VGAM341 is therefore inhibition of Gap Junction Protein, Alpha 1, 43kDa (connexin 43) (GJA1, Accession NM\_000165), a gene which may act in synchronizing heart contraction and embryonic development. Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GJA1. The function of GJA1 has been established by previous studies. The migration of lymphocytes from the circulation into tissues involves a number of ad-



hesion molecules and the expression of new molecules. Gap junctions facilitate cell-to-cell adhesion and provide pathways for direct intercellular communication. Oviedo-Orta et al. (2000) noted that GJA1 is expressed in a number of lymphoid organs. By RT-PCR, Western blot, and flow cytometric analyses, they showed that lymphocytes express GJA1 and GJA5 (OMIM Ref. No. 121013), but not GJB2 (OMIM Ref. No. 121011), GJB1 (OMIM Ref. No. 304040), GJA4 (OMIM Ref. No. 121012), or GJA7; GJA5 expression was restricted to tonsillar T and B lymphocytes. Flow cytometric analysis showed that GJA1 and GJA5 expression increases after mitogenic stimulation. Extracellular connexin mimetic peptide blocked dye transfer between lymphocyte subpopulations, and gap junction inhibitors decreased the production of IgM in cocultured T and B lymphocytes. The results identified gap junction proteins as important cell surface components that modulate immune responses. Animal model experiments lend further support to the function of GJA1. By targeted mutagenesis of connexin-43, Reaume et al. (1995) showed that its absence was compatible with survival of mouse embryos to term, even though cell lines mutant in Cx43 showed reduced dye coupling in vitro as assessed by in-

jection of carboxyfluorescein. The latter test indicated a reduction, but not complete absence, of junctional communication. However, mutant embryos died at birth as a result of a failure in pulmonary gas exchange caused by a swelling and blockage of the right ventricular outflow tract from the heart. Reaume et al. (1995) interpreted this finding as indicating that Cx43 plays an essential role in heart development but that there is functional compensation among connexins in other parts of the developing fetus.

[17731] It is appreciated that the abovementioned animal model for GJA1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[17732] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17733] Oviedo-Orta, E.; Hoy, T.; Evans, W. H. : Intercellular communication in the immune system: differential expression of connexin40 and 43, and perturbation of gap junction channel functions in peripheral blood and tonsil human lymphocyte subpopulations. Immunology 99: 578-590, 2000. ; and

[17734] Reaume, A. G.; de Sousa, P. A.; Kulkarni, S.; Langille, B. L.;

Zhu, D.; Davies, T. C.; Juneja, S. C.; Kidder, G. M.; Rossant, J. : Cardiac malformation in neonatal mice lacking connex.

[17735] Further studies establishing the function and utilities of GJA1 are found in John Hopkins OMIM database record ID 121014, and in cited publications numbered 11845–11850, 11978, 136–139, 12142–142, 11843–145, 145–14 and 11839 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Host Cell Factor C1 (VP16–accessory protein) (HCFC1, Accession XM\_048390) is another VGAM341 host target gene. HCFC1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HCFC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCFC1 BINDING SITE, designated SEQ ID:35156, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17736] Another function of VGAM341 is therefore inhibition of Host Cell Factor C1 (VP16–accessory protein) (HCFC1, Accession XM\_048390), a gene which is a host cell factor, has a role in cell proliferation and can form a complex

with HSV VP16. Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCFC1. The function of HCFC1 has been established by previous studies. By fluorescence in situ hybridization and somatic cell hybrid analysis, Wilson et al. (1995) mapped the HCFC1 gene to Xq28. YAC and cosmid mapping localized the HCFC1 gene within 100 kb distal of the V2R gene (OMIM Ref. No. 304800) and adjacent to the renin-binding protein gene (OMIM Ref. No. 312420). HCF transcripts and protein are most abundant in fetal and placental tissues and cell lines, suggesting a role in cell proliferation. In adults, HCF protein is abundant in the kidney, but not in the brain, a site of latent herpes simplex virus (HSV) infection and a site where HCF levels may influence progression of HSV infection. Zoppe et al. (1996) reported the complete sequence of the HCFC1 gene, including 2 kb of the 5-prime-flanking region and 5.9 kb of the first intron. In addition to the detection of many putative binding sites for known DNA binding proteins, a highly conserved 17-bp sequence was found to be present 6 times at regular intervals in the 5-prime region of the gene. This motif is capable of binding the transcription factor Yin/Yang 1

(YY1) as well as another unidentified factor, suggesting that HCFC1 expression is regulated by the interaction of these factors.

[17737] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17738] Wilson, A. C.; Parrish, J. E.; Massa, H. F.; Nelson, D. L.; Trask, B. J.; Herr, W. : The gene encoding the VP16-accessory protein HCF (HCFC1) resides in human Xq28 and is highly expressed in fetal tissues and the adult kidney. Genomics 25: 462-468, 1995. ; and

[17739] Zoppe, M.; Frattini, A.; Faranda, S.; Vezzoni, P. : The complete sequence of the host cell factor 1 (HCFC1) gene and its promoter: a role for YY1 transcription factor in the regulation o.

[17740] Further studies establishing the function and utilities of HCFC1 are found in John Hopkins OMIM database record ID 300019, and in cited publications numbered 7265-7270 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neurotrophic Tyrosine Kinase, Receptor, Type 2 (NTRK2, Accession NM\_006180) is another VGAM341 host target gene. NTRK2 BINDING SITE is HOST TARGET binding

site found in the 3' untranslated region of mRNA encoded by NTRK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NTRK2 BINDING SITE, designated SEQ ID:12850, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17741] Another function of VGAM341 is therefore inhibition of Neurotrophic Tyrosine Kinase, Receptor, Type 2 (NTRK2, Accession NM\_006180), a gene which is involved in the development and/or maintenance of the nervous system. Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NTRK2. The function of NTRK2 has been established by previous studies. Nakagawara et al. (1995) isolated cDNAs spanning the entire coding region of both human full-length and truncated forms of TRKB from human brain cDNA libraries. The full-length TRKB coded for a protein of 822 amino acid residues. The putative mature peptide sequence was 49% and 55% homologous to human NTRK1 and NTRK3, respectively. Nine of 13 cysteine residues, 4 of 12 N-glycosylation sites in the extracellular

domain, and 10 of 13 tyrosine residues in the intracellular domain are conserved among NTRK1, NTRK2, and NTRK3. Two major sizes of NTRK2 transcripts were expressed in human brain. Animal model experiments lend further support to the function of NTRK2. To study the function of TRKB in the cerebellum, Rico et al. (2002) deleted the *Trkb* gene in mouse cerebellar precursors by Wnt1-driven Cre-mediated recombination. Despite the absence of *Trkb*, the mature cerebellum of mutant mice appeared similar to that of wildtype, with all types of cells present in normal numbers and positions. Granule and Purkinje cell dendrites appeared normal, and the former had typical numbers of excitatory synapses. By contrast, inhibitory interneurons were strongly affected. Although present in normal number, inhibitory interneurons exhibited reduced amounts of GABAergic markers and developed reduced numbers of GABAergic boutons and synaptic specializations. Thus, Rico et al. (2002) concluded that TRKB is essential to the development of GABAergic neurons and regulates synapse formation in addition to its role in the development of axon terminals.

[17742] It is appreciated that the abovementioned animal model for NTRK2 is acknowledged by those skilled in the art as a

scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[17743] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17744] Nakagawara, A.; Liu, X.-G.; Ikegaki, N.; White, P. S.; Yamashiro, D. J.; Nycum, L. M.; Biegel, J. A.; Brodeur, G. M. : Cloning and chromosomal localization of the human TRK-B tyrosine kinase receptor gene (NTRK2). *Genomics* 25: 538–546, 1995. ; and

[17745] Rico, B.; Xu, B.; Reichardt, L. F. : TrkB receptor signaling is required for establishment of GABAergic synapses in the cerebellum. *Nature Neurosci.* 5: 225–233, 2002.

[17746] Further studies establishing the function and utilities of NTRK2 are found in John Hopkins OMIM database record ID 600456, and in cited publications numbered 1939–1940, 1942, 12375–161 and 12342 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Proteasome (prosome, macropain) 26S Subunit, Non-ATPase, 5 (PSMD5, Accession NM\_005047) is another VGAM341 host target gene. PSMD5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by



PSMD5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSMD5 BINDING SITE, designated SEQ ID:11480, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17747] Another function of VGAM341 is therefore inhibition of Proteasome (prosome, macropain) 26S Subunit, Non-ATPase, 5 (PSMD5, Accession NM\_005047), a gene which is the non-ATPase subunit 5 of the 26S proteasome (prosome macropain). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSMD5. The function of PSMD5 has been established by previous studies. The covalent attachment of ubiquitin to proteins produces substrates for the 26S ATP-dependent protease. This enzyme is composed of the multicatalytic protease, or proteasome, and a regulatory ATPase complex. Both the multicatalytic protease and the regulatory complex are multi-subunit structures that associate in the presence of ATP to form the 26S enzyme. Deveraux et al. (1994) identified a 50-kD subunit of the regulatory complex, which they

called subunit 5 (S5) based upon its relative mobility on SDS–polyacrylamide gels. Deveraux et al. (1995) demonstrated that 2 distinct subunits of the 26S protease migrate as 50–kD proteins, and thus, S5 represents 2 proteins, which the authors termed S5A (PSMD4; 601648) and S5B, also called PSMD5. Deveraux et al. (1995) sequenced peptides from the PSMD5 subunit of the human red blood cell 26S protease. Using the amino acid sequence, they isolated human cDNAs comprising a full–length PSMD5 cDNA. The deduced 505–amino acid PSMD5 protein is enriched in leucine residues, particularly in the N–terminal region. PSMD5 contains 9 dileucine repeats and a sequence, NPNY, similar to the tyrosine–based motifs. Dileucine repeats and tyrosine–based motifs are thought to contribute to internalization and/or targeting. PSMD5 has a calculated molecular mass of 56 kD and focuses at pH 5.3 on 2–dimensional gels. Recombinant PSMD5 did not bind to ubiquitin polymers. By sequencing cDNAs randomly selected from a cDNA library derived from a human immature myeloid cell line, Nomura et al. (1994) isolated a partial cDNA encoding PSMD5, which they called KIAA0072. Northern blot analysis detected PSMD5 expression in a wide variety of human tissues, with the highest

expression in lung and skeletal muscle. Deveraux et al. (1995) noted that the nucleotide sequence of the KIAA0072 cDNA is identical to the corresponding nucleotide sequence of the S5B cDNA.

[17748] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17749] Deveraux, Q.; Jensen, C.; Rechsteiner, M. : Molecular cloning and expression of a 26 S protease subunit enriched in dileucine repeats. J. Biol. Chem. 270: 23726–23729, 1995. ; and

[17750] Deveraux, Q.; Ustrell, V.; Pickart, C.; Rechsteiner, M. : A 26 S protease subunit that binds ubiquitin conjugates. J. Biol. Chem. 269: 7059–7061, 1994.

[17751] Further studies establishing the function and utilities of PSMD5 are found in John Hopkins OMIM database record ID 604452, and in cited publications numbered 6555–655 and 2255 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Retinal Degeneration, Slow (retinitis pigmentosa 7) (RDS, Accession NM\_000322) is another VGAM341 host target gene. RDS BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RDS, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RDS BINDING SITE, designated SEQ ID:5864, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17752] Another function of VGAM341 is therefore inhibition of Retinal Degeneration, Slow (retinitis pigmentosa 7) (RDS, Accession NM\_000322), a gene which may function as an adhesion molecule involved in stabilization and compaction of outer segment disks or in the maintenance of the curvature of the rim. Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RDS. The function of RDS has been established by previous studies. In mammals, most cyanide is converted to thiocyanate by the mitochondrial enzyme thiosulfate sulfurtransferase. Cagianut et al. (1981) found much reduced activity of this enzyme in the livers of 2 males with Leber optic atrophy (OMIM Ref. No. 535000) from a well-studied Swiss family with 5 symptomatic persons in 4 generations. Nikoskelainen (1984) could not confirm the reported low activity of rhodanese in Leber patients. Whitehouse et al. (1989)

studied rhodanese isozymes in liver biopsies from 3 subjects with Leber optic neuropathy. No qualitative abnormality and no deficiency could be found, thus excluding the hypothesis of rhodanese deficiency. By screening a human fetal liver cDNA expression library with a monoclonal antibody against bovine liver rhodanese, Aita et al. (1997) cloned a RDS cDNA. Northern blotting showed that the RDS gene is expressed as a 1.3-kb mRNA. It encodes a predicted 297-amino acid protein that is approximately 90% identical to rodent and bovine Rds. Transient expression of the RDS cDNA in *E. coli* and in mammalian cells resulted in significantly increased rhodanese activity. Animal model experiments lend further support to the function of RDS.

[17753] It is appreciated that the abovementioned animal model for RDS is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[17754] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17755] Whitehouse, D. B.; Poole, C. J. M.; Kind, P. R. N.; Hopkinson, D. A. : Rhodanese isozymes in three subjects with

Leber's optic neuropathy. J. Med. Genet. 26: 113–115, 1989. ; and

[17756] Aita, N.; Ishii, K.; Akamatsu, Y.; Ogasawara, Y.; Tanabe, S. : Cloning and expression of human liver rhodanese cDNA. Biochem. Biophys. Res. Commun. 231: 56–60, 1997.

[17757] Further studies establishing the function and utilities of RDS are found in John Hopkins OMIM database record ID 180370, and in cited publications numbered 2552–255 and 11874–2558 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transmembrane, Prostate Androgen Induced RNA (TMEPAI, Accession NM\_020182) is another VGAM341 host target gene. TMEPAI BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMEPAI, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMEPAI BINDING SITE, designated SEQ ID:21408, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17758] Another function of VGAM341 is therefore inhibition of Transmembrane, Prostate Androgen Induced RNA

(TMEPAI, Accession NM\_020182). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMEPAI. Tripartite Motif-containing 9 (TRIM9, Accession NM\_015163) is another VGAM341 host target gene. TRIM9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM9 BINDING SITE, designated SEQ ID:17513, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17759] Another function of VGAM341 is therefore inhibition of Tripartite Motif-containing 9 (TRIM9, Accession NM\_015163), a gene which may function as a positive regulator for mannosylphosphate transferase and is required to mediate mannosylphosphate transfer in both the core and outer chain portions of n-linked oligosaccharides. Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM9. The function of TRIM9 and its association with various diseases and clinical condi-

tions, has been established by previous studies, as described hereinabove with reference to VGAM74. Blepharophimosis, Epicanthus Inversus and Pto- sis, Candidate 1 (BPESC1, Accession NM\_021812) is another VGAM341 host target gene. BPESC1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by BPESC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND- ING SITE II or BINDING SITE III. Table 2 illustrates the com- plementarity of the nucleotide sequences of BPESC1 BIND- ING SITE, designated SEQ ID:22375, to the nucleotide se- quence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17760] Another function of VGAM341 is therefore inhibition of Blepharophimosis, Epicanthus Inversus and Pto- sis, Candi- date 1 (BPESC1, Accession NM\_021812). Accordingly, util- ities of VGAM341 include diagnosis, prevention and treat- ment of diseases and clinical conditions associated with BPESC1. Chromosome 1 Open Reading Frame 22 (C1orf22, Accession NM\_025191) is another VGAM341 host target gene. C1orf22 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C1orf22, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1orf22 BINDING SITE, designated SEQ ID:24836, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17761] Another function of VGAM341 is therefore inhibition of Chromosome 1 Open Reading Frame 22 (C1orf22, Accession NM\_025191). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf22. FLJ14075 (Accession NM\_024894) is another VGAM341 host target gene. FLJ14075 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14075, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14075 BINDING SITE, designated SEQ ID:24375, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17762] Another function of VGAM341 is therefore inhibition of FLJ14075 (Accession NM\_024894). Accordingly, utilities of

VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14075. KIAA0852 (Accession NM\_014941) is another VGAM341 host target gene. KIAA0852 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA0852, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0852 BINDING SITE, designated SEQ ID:17249, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17763] Another function of VGAM341 is therefore inhibition of KIAA0852 (Accession NM\_014941). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0852. KIAA1203 (Accession XM\_049683) is another VGAM341 host target gene. KIAA1203 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1203, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1203 BINDING SITE, designated SEQ ID:35469, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17764] Another function of VGAM341 is therefore inhibition of KIAA1203 (Accession XM\_049683). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1203. Mitogen-activated Protein Kinase Kinase Kinase 2 (MAP3K2, Accession NM\_006609) is another VGAM341 host target gene. MAP3K2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAP3K2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP3K2 BINDING SITE, designated SEQ ID:13387, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17765] Another function of VGAM341 is therefore inhibition of Mitogen-activated Protein Kinase Kinase Kinase 2 (MAP3K2, Accession NM\_006609). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP3K2.

Roundabout Homolog 4, Magic Roundabout (Drosophila) (ROBO4, Accession NM\_019055) is another VGAM341 host target gene. ROBO4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ROBO4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ROBO4 BINDING SITE, designated SEQ ID:21136, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17766] Another function of VGAM341 is therefore inhibition of Roundabout Homolog 4, Magic Roundabout (Drosophila) (ROBO4, Accession NM\_019055). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ROBO4. SE70-2 (Accession NM\_022118) is another VGAM341 host target gene. SE70-2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SE70-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SE70-2 BINDING SITE, designated

SEQ ID:22665, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17767] Another function of VGAM341 is therefore inhibition of SE70-2 (Accession NM\_022118). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SE70-2. TTY7 (Accession NM\_031926) is another VGAM341 host target gene. TTY7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TTY7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TTY7 BINDING SITE, designated SEQ ID:25674, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17768] Another function of VGAM341 is therefore inhibition of TTY7 (Accession NM\_031926). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TTY7. LOC130074 (Accession XM\_072228) is another VGAM341 host target gene. LOC130074 BINDING SITE is HOST TAR-

GET binding site found in the 3' untranslated region of mRNA encoded by LOC130074, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130074 BINDING SITE, designated SEQ ID:37472, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17769] Another function of VGAM341 is therefore inhibition of LOC130074 (Accession XM\_072228). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130074. LOC152457 (Accession XM\_087476) is another VGAM341 host target gene. LOC152457 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152457, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152457 BINDING SITE, designated SEQ ID:39278, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17770] Another function of VGAM341 is therefore inhibition of

LOC152457 (Accession XM\_087476). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152457. LOC170106 (Accession XM\_093106) is another VGAM341 host target gene. LOC170106 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC170106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170106 BINDING SITE, designated SEQ ID:40174, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17771] Another function of VGAM341 is therefore inhibition of LOC170106 (Accession XM\_093106). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170106. LOC200860 (Accession XM\_117289) is another VGAM341 host target gene. LOC200860 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200860, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC200860 BINDING SITE, designated SEQ ID:43358, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17772] Another function of VGAM341 is therefore inhibition of LOC200860 (Accession XM\_117289). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200860. LOC221300 (Accession XM\_166322) is another VGAM341 host target gene. LOC221300 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221300, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221300 BINDING SITE, designated SEQ ID:44149, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17773] Another function of VGAM341 is therefore inhibition of LOC221300 (Accession XM\_166322). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221300. LOC90161 (Accession XM\_029551) is an-



other VGAM341 host target gene. LOC90161 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90161, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90161 BINDING SITE, designated SEQ ID:30903, to the nucleotide sequence of VGAM341 RNA, herein designated VGAM RNA, also designated SEQ ID:3052.

[17774] Another function of VGAM341 is therefore inhibition of LOC90161 (Accession XM\_029551). Accordingly, utilities of VGAM341 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90161. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 342 (VGAM342) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17775] VGAM342 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM342 was detected is described

hereinabove with reference to Figs. 1–8.

[17776] VGAM342 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tobacco Mosaic Virus.

VGAM342 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[17777] VGAM342 gene encodes a VGAM342 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM342 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM342 precursor RNA is designated SEQ ID:328, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:328 is located at position 3311 relative to the genome of Tobacco Mosaic Virus.

[17778] VGAM342 precursor RNA folds onto itself, forming VGAM342 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17779] An enzyme complex designated DICER COMPLEX, `dices` the VGAM342 folded precursor RNA into VGAM342 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM342 RNA is designated SEQ ID:3053, and is provided hereinbelow with reference to the sequence listing part.

[17780] VGAM342 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM342 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM342 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17781] VGAM342 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM342 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM342 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM342 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM342 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17782] The complementary binding of VGAM342 RNA, herein designated VGAM RNA, to host target binding sites on VGAM342 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM342 host target RNA into VGAM342 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17783] It is appreciated that VGAM342 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM342 host target genes. The mRNA of each one of this plurality of VGAM342 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM342 RNA, herein designated VGAM RNA, and which when bound by VGAM342 RNA causes inhibition of translation of respective one or more VGAM342 host target proteins.

[17784] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM342 gene, herein designated VGAM GENE, on one or more VGAM342 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17785] It is yet further appreciated that a function of VGAM342 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of viral infection by Tobacco Mosaic Virus. Specific functions, and accordingly utilities, of VGAM342 correlate with, and may be deduced from, the identity of the host target genes which VGAM342 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[17786] Nucleotide sequences of the VGAM342 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM342 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM342 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM342 are further described hereinbelow with reference to Table 1.

[17787] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM342 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM342 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17788] As mentioned hereinabove with reference to Fig. 1, a function of VGAM342 gene, herein designated VGAM is inhibition of expression of VGAM342 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM342 correlate with, and may be deduced from, the identity of the target genes which VGAM342 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17789] Membrane Protein, Palmitoylated 2 (MAGUK p55 subfamily member 2) (MPP2, Accession XM\_008355) is a VGAM342 host target gene. MPP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MPP2, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MPP2 BINDING SITE, designated SEQ ID:30078, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17790] A function of VGAM342 is therefore inhibition of Membrane Protein, Palmitoylated 2 (MAGUK p55 subfamily member 2) (MPP2, Accession XM\_008355). Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MPP2. RPP30 (Accession NM\_006413) is another VGAM342 host target gene. RPP30 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RPP30, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RPP30 BINDING SITE, designated SEQ ID:13121, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17791] Another function of VGAM342 is therefore inhibition of RPP30 (Accession NM\_006413), a gene which is a compo-



ment of ribonuclease p that processes 5' ends of precursor tRNAs. Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RPP30. The function of RPP30 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM230. Tumor-associated Calcium Signal Transducer 2 (TACSTD2, Accession NM\_002353) is another VGAM342 host target gene. TACSTD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TACSTD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TACSTD2 BINDING SITE, designated SEQ ID:8158, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17792] Another function of VGAM342 is therefore inhibition of Tumor-associated Calcium Signal Transducer 2 (TACSTD2, Accession NM\_002353), a gene which belongs to ga733 tumor-associated antigen gene family and may function as growth factor receptors. Accordingly, utilities

of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TACSTD2. The function of TACSTD2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM210. Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445) is another VGAM342 host target gene. GRIN3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRIN3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRIN3A BINDING SITE, designated SEQ ID:28529, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17793] Another function of VGAM342 is therefore inhibition of Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445). Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRIN3A. P5-1 (Accession NM\_006674) is another VGAM342 host target gene. P5-1 BINDING SITE is HOST TARGET binding

site found in the 3` untranslated region of mRNA encoded by P5-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P5-1 BINDING SITE, designated SEQ ID:13494, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17794] Another function of VGAM342 is therefore inhibition of P5-1 (Accession NM\_006674). Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P5-1. POLD3 (Accession XM\_166243) is another VGAM342 host target gene. POLD3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by POLD3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POLD3 BINDING SITE, designated SEQ ID:44054, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17795] Another function of VGAM342 is therefore inhibition of

POLD3 (Accession XM\_166243). Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POLD3. LOC147639 (Accession XM\_085822) is another VGAM342 host target gene. LOC147639 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147639, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147639 BINDING SITE, designated SEQ ID:38347, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17796] Another function of VGAM342 is therefore inhibition of LOC147639 (Accession XM\_085822). Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147639. LOC154282 (Accession XM\_098505) is another VGAM342 host target gene. LOC154282 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154282, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC154282 BINDING SITE, designated SEQ ID:41696, to the nucleotide sequence of VGAM342 RNA, herein designated VGAM RNA, also designated SEQ ID:3053.

[17797] Another function of VGAM342 is therefore inhibition of LOC154282 (Accession XM\_098505). Accordingly, utilities of VGAM342 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154282. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 343 (VGAM343) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17798] VGAM343 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM343 was detected is described hereinabove with reference to Figs. 1–8.

[17799] VGAM343 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tobacco Mosaic Virus. VGAM343 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[17800] VGAM343 gene encodes a VGAM343 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM343 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM343 precursor RNA is designated SEQ ID:329, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:329 is located at position 1903 relative to the genome of Tobacco Mosaic Virus.

[17801] VGAM343 precursor RNA folds onto itself, forming VGAM343 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17802] An enzyme complex designated DICER COMPLEX, `dices` the VGAM343 folded precursor RNA into VGAM343 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM343 RNA is designated SEQ ID:3054, and is provided hereinbelow with reference to the sequence listing part.

[17803] VGAM343 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM343 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM343 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17804] VGAM343 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM343 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM343 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM343 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM343 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17805] The complementary binding of VGAM343 RNA, herein designated VGAM RNA, to host target binding sites on VGAM343 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM343 host target RNA into VGAM343 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.



[17806] It is appreciated that VGAM343 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM343 host target genes. The mRNA of each one of this plurality of VGAM343 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM343 RNA, herein designated VGAM RNA, and which when bound by VGAM343 RNA causes inhibition of translation of respective one or more VGAM343 host target proteins.

[17807] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM343 gene, herein designated VGAM GENE, on one or more VGAM343 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17808] It is yet further appreciated that a function of VGAM343 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM343 include diagnosis, prevention and treatment of viral infection by Tobacco Mosaic Virus. Specific functions, and accordingly utilities, of VGAM343 correlate with, and may be deduced from, the identity of the host target genes which VGAM343 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[17809] Nucleotide sequences of the VGAM343 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM343 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM343 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM343 are further described hereinbelow with reference to Table 1.

[17810] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM343 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM343 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17811] As mentioned hereinabove with reference to Fig. 1, a function of VGAM343 gene, herein designated VGAM is inhibition of expression of VGAM343 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM343 correlate with, and may be deduced from, the identity of the target genes which VGAM343 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17812] Immediate Early Response 5 (IER5, Accession NM\_016545) is a VGAM343 host target gene. IER5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IER5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IER5 BINDING SITE, designated SEQ ID:18611, to the nucleotide sequence of VGAM343 RNA, herein designated VGAM RNA, also designated SEQ ID:3054.

[17813] A function of VGAM343 is therefore inhibition of Immediate Early Response 5 (IER5, Accession NM\_016545), a gene which may play an important role in mediating the cellular response to mitogenic signals. Accordingly, utilities of VGAM343 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IER5. The function of IER5 has been established by previous studies. Williams et al. (1999) cloned a novel member of the slow-kinetics immediate-early response gene family, designated *Ier5*, from a mouse brain cDNA library. Mouse *Ier5* encodes a deduced 308-amino acid protein with a predicted molecular mass of 31.9 kD. The N-terminal 49 amino acids show 57% sequence identity with those of the *Ier2* protein. *Ier5* contains 3 potential nuclear targeting signals, a possible PEST sequence, which suggests rapid protein degradation, and several potential phosphorylation sites. Northern blot analysis of total cellular RNA from serum-starved NIH 3T3 cells showed no detectable transcription in quiescent cells, but detected a single transcript within 30 minutes after exposure to serum. Transcription was also stimulated by the growth factors TPA (OMIM Ref. No. 173370), FGF (see OMIM Ref. No. 131220), and PDGF (see OMIM Ref. No. 173430), and

did not appear to be dependent on protein kinase C (see OMIM Ref. No. 176960) activity. Williams et al. (1999) identified 2 possible Ets-1 sites, a number of potential Sp1 sites, and 3 potential AP1-binding sites in the promoter region of the mouse *Ier5* gene. The *IER5* genes in humans and mice are highly homologous to their counterpart in zebrafish. In all of these organisms, *IER5* is an intronless gene (Gottgens et al., 2002). The International Radiation Hybrid Mapping Consortium mapped the *IER5* gene to chromosome 1 (stSG23644).

[17814] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17815] Gottgens, B.; Barton, L. M.; Chapman, M. A.; Sinclair, A. M.; Knudsen, B.; Grafham, D.; Gilbert, J. G. R.; Rogers, J.; Bentley, D. R.; Green, A. R. : Transcriptional regulation of the stem cell leukemia gene (*SCL*)--comparative analysis of five vertebrate *SCL* loci. *Genome Res.* 12: 749-759, 2002. ; and

[17816] Williams, M.; Lyu, M.-S.; Yang, Y.-L.; Lin, E. P.; Dunbrack, R.; Birren, B.; Cunningham, J.; Hunter, K. : *Ier5*, a novel member of the slow-kinetics immediate-early genes. *Genomics* 55: 3.

[17817] Further studies establishing the function and utilities of IER5 are found in John Hopkins OMIM database record ID 607177, and in cited publications numbered 251 and 5542 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC149535 (Accession XM\_086567) is another VGAM343 host target gene. LOC149535 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149535, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149535 BINDING SITE, designated SEQ ID:38770, to the nucleotide sequence of VGAM343 RNA, herein designated VGAM RNA, also designated SEQ ID:3054.

[17818] Another function of VGAM343 is therefore inhibition of LOC149535 (Accession XM\_086567). Accordingly, utilities of VGAM343 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149535. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 344 (VGAM344) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17819] VGAM344 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM344 was detected is described hereinabove with reference to Figs. 1–8.

[17820] VGAM344 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tobacco Mosaic Virus. VGAM344 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[17821] VGAM344 gene encodes a VGAM344 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM344 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM344 precursor RNA is designated SEQ ID:330, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:330 is located at position 2117 relative to the genome of Tobacco Mosaic Virus.

[17822] VGAM344 precursor RNA folds onto itself, forming

VGAM344 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17823] An enzyme complex designated DICER COMPLEX, `dices` the VGAM344 folded precursor RNA into VGAM344 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM344 RNA is designated SEQ ID:3055, and is provided hereinbelow with reference to the sequence listing part.

[17824] VGAM344 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM344 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM344 host target RNA comprises



three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[17825] VGAM344 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM344 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM344 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM344 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM344 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17826] The complementary binding of VGAM344 RNA, herein designated VGAM RNA, to host target binding sites on VGAM344 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM344 host target RNA into VGAM344 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17827] It is appreciated that VGAM344 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM344 host target genes. The mRNA of each one of this plurality of VGAM344 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM344 RNA, herein designated VGAM RNA, and which when bound by VGAM344 RNA causes inhibition of translation of respective one or more VGAM344 host target proteins.

[17828] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM344 gene, herein designated VGAM GENE, on one or more VGAM344 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17829] It is yet further appreciated that a function of VGAM344 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM344 include diagnosis, prevention and treatment of viral infection by Tobacco Mosaic Virus. Specific functions, and accordingly utilities, of VGAM344 correlate with, and may be deduced from, the identity of the host target genes which VGAM344 binds and inhibits, and

the function of these host target genes, as elaborated hereinbelow.

[17830] Nucleotide sequences of the VGAM344 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM344 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM344 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM344 are further described hereinbelow with reference to Table 1.

[17831] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM344 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM344 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17832] As mentioned hereinabove with reference to Fig. 1, a function of VGAM344 gene, herein designated VGAM is inhibition of expression of VGAM344 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM344 correlate with, and may be deduced from, the identity of the target genes which VGAM344 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[17833] Fms-related Tyrosine Kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor) (FLT1, Accession NM\_002019) is a VGAM344 host target gene. FLT1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLT1 BINDING SITE, designated SEQ ID:7766, to the nucleotide sequence of VGAM344 RNA, herein designated VGAM RNA, also designated SEQ ID:3055.

[17834] A function of VGAM344 is therefore inhibition of Fms-related Tyrosine Kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor) (FLT1, Accession NM\_002019). Accordingly, utilities of VGAM344 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLT1. Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698) is another VGAM344 host target gene. BLCAP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by BLCAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLCAP BINDING SITE, designated SEQ ID:13518, to the nucleotide sequence of VGAM344 RNA, herein designated VGAM RNA, also designated SEQ ID:3055.

[17835] Another function of VGAM344 is therefore inhibition of Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698). Accordingly, utilities of VGAM344 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLCAP. KIAA0711 (Accession NM\_014867) is another VGAM344 host target gene. KIAA0711 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0711, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0711 BINDING SITE, designated SEQ ID:16954, to the nucleotide sequence of VGAM344 RNA, herein designated VGAM RNA, also designated SEQ ID:3055.

[17836] Another function of VGAM344 is therefore inhibition of KIAA0711 (Accession NM\_014867). Accordingly, utilities of VGAM344 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0711. LOC135293 (Accession XM\_072402) is another VGAM344 host target gene. LOC135293 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC135293, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC135293 BINDING SITE, designated SEQ ID:37491, to the nucleotide sequence of VGAM344 RNA, herein designated VGAM RNA, also designated SEQ ID:3055.

[17837] Another function of VGAM344 is therefore inhibition of LOC135293 (Accession XM\_072402). Accordingly, utilities of VGAM344 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC135293. LOC222962 (Accession XM\_167291) is another VGAM344 host target gene. LOC222962 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC222962, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222962 BINDING SITE, designated SEQ ID:44625, to

the nucleotide sequence of VGAM344 RNA, herein designated VGAM RNA, also designated SEQ ID:3055.

[17838] Another function of VGAM344 is therefore inhibition of LOC222962 (Accession XM\_167291). Accordingly, utilities of VGAM344 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222962. LOC92973 (Accession XM\_048529) is another VGAM344 host target gene. LOC92973 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92973, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92973 BINDING SITE, designated SEQ ID:35183, to the nucleotide sequence of VGAM344 RNA, herein designated VGAM RNA, also designated SEQ ID:3055.

[17839] Another function of VGAM344 is therefore inhibition of LOC92973 (Accession XM\_048529). Accordingly, utilities of VGAM344 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92973. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-



dress Messenger 345 (VGAM345) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17840] VGAM345 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM345 was detected is described hereinabove with reference to Figs. 1–8.

[17841] VGAM345 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Adenovirus C. VGAM345 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[17842] VGAM345 gene encodes a VGAM345 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM345 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM345 precursor RNA is designated SEQ ID:331, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:331 is located at position 19970 relative to the genome of Human Adenovirus C.

[17843] VGAM345 precursor RNA folds onto itself, forming VGAM345 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17844] An enzyme complex designated DICER COMPLEX, `dices` the VGAM345 folded precursor RNA into VGAM345 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM345 RNA is designated SEQ ID:3056, and is provided hereinbelow with reference to the sequence listing part.

[17845] VGAM345 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM345 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM345 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17846] VGAM345 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM345 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM345 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM345 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM345 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17847] The complementary binding of VGAM345 RNA, herein designated VGAM RNA, to host target binding sites on VGAM345 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM345 host target RNA into VGAM345 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17848] It is appreciated that VGAM345 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM345 host target genes. The mRNA of each one of this plurality of VGAM345 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM345 RNA, herein designated VGAM RNA, and which when bound by VGAM345 RNA causes inhibition of translation of respective one or more VGAM345 host target proteins.

[17849] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM345 gene, herein designated VGAM GENE, on one or more VGAM345 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17850] It is yet further appreciated that a function of VGAM345 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of viral infection by Human Adenovirus C. Specific functions, and accordingly utilities, of VGAM345 correlate with, and may be deduced from, the identity of the

host target genes which VGAM345 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[17851] Nucleotide sequences of the VGAM345 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM345 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM345 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM345 are further described hereinbelow with reference to Table 1.

[17852] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM345 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM345 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17853] As mentioned hereinabove with reference to Fig. 1, a function of VGAM345 gene, herein designated VGAM is inhibition of expression of VGAM345 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM345 correlate with, and may be deduced from, the identity of the target genes which VGAM345

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17854] Aryl–hydrocarbon Receptor Nuclear Translocator 2 (ARNT2, Accession NM\_014862) is a VGAM345 host target gene. ARNT2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ARNT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARNT2 BINDING SITE, designated SEQ ID:16933, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17855] A function of VGAM345 is therefore inhibition of Aryl–hydrocarbon Receptor Nuclear Translocator 2 (ARNT2, Accession NM\_014862), a gene which specifically recognizes the xenobiotic response element (xre). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARNT2. The function of ARNT2 has been established by previous studies. Hirose et al. (1996) determined that Arnt2 interacts with mouse AhR and Sim as efficiently as Arnt and that the Arnt2–AhR complex recognizes and

specifically binds the xenobiotic responsive element (XRE) sequence. In DNA transfection experiments, Arnt2 rescued XRE-driven reporter gene activity in Arnt mutant cells. RNA blot analysis detected restricted expression of Arnt2 in the brains and kidneys of adult mice, in contrast to the ubiquitous expression of Arnt. In situ hybridization experiments demonstrated expression of Arnt2 exclusively in the dorsal region of the spinal cord and branchial arch-1, whereas Arnt expression was broadly distributed in the ventral portion of the mesodermal and endodermal tissues. Animal model experiments lend further support to the function of ARNT2. To assess the role of ARNT2 in development and determine functional overlap with ARNT, Keith et al. (2001) generated a targeted null mutation of the murine Arnt2 locus. Arnt2  $-/-$  embryos died perinatally and exhibited impaired hypothalamic development, phenotypes previously observed for a targeted mutation in the murine Sim1 gene and consistent with the proposal by Michaud et al. (2000) that Arnt2 and Sim1 form an essential heterodimer in vivo. In addition, cultured Arnt2  $-/-$  neurons displayed decreased hypoxic induction of HIF1A target genes, demonstrating formally that ARNT2/HIF1A complexes regulate oxygen-responsive genes. Finally, a



strong genetic interaction between Arnt and Arnt2 mutations was observed, indicating that either gene can fulfill essential functions in a dose-dependent manner before embryonic day 8.5. These results demonstrated that Arnt and Arnt2 have both unique and overlapping essential functions in embryonic development.

[17856] It is appreciated that the abovementioned animal model for ARNT2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[17857] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17858] Hirose, K.; Morita, M.; Ema, M.; Mimura, J.; Hamada, H.; Fujii, H.; Saijo, Y.; Gotoh, O.; Sogawa, K.; Fujii-Kuriyama, Y. : cDNA cloning and tissue-specific expression of a novel basic helix-loop-helix/PAS factor (Arnt2) with close sequence similarity to the aryl hydrocarbon receptor nuclear translocator (Arnt). *Molec. Cell. Biol.* 16: 1706-1713, 1996. ; and

[17859] Keith, B.; Adelman, D. M.; Simon, M. C. : Targeted mutation of the murine arylhydrocarbon receptor nuclear translocator 2 (Arnt2) gene reveals partial redundancy

with Arnt. Proc. Nat. Ac.

[17860] Further studies establishing the function and utilities of ARNT2 are found in John Hopkins OMIM database record ID 606036, and in cited publications numbered 6445–644 and 957 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RalA Binding Protein 1 (RALBP1, Accession NM\_006788) is another VGAM345 host target gene. RALBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RALBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RALBP1 BINDING SITE, designated SEQ ID:13657, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17861] Another function of VGAM345 is therefore inhibition of RalA Binding Protein 1 (RALBP1, Accession NM\_006788), a gene which plays a role in signal transduction and catalyzes the transport of glutathione conjugates and xenobiotics. Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RALBP1. The function of RALBP1

has been established by previous studies. Small G proteins have GDP-bound inactive and GTP-bound active forms; RAL proteins (e.g., RALA; 179550) shift from the inactive to the active state through the actions of RALGDS (OMIM Ref. No. 601619). RALGDS interacts with the active form of RAS (see OMIM Ref. No. HRAS; 190020). Using a mutant form of RALA lacking the C-terminal 27 amino acids as bait in a yeast 2-hybrid screen of a Jurkat cDNA library, followed by 5-prime RACE and screening skeletal muscle and placenta cDNA libraries, Jullien-Flores et al. (1995) obtained a cDNA encoding RALBP1, which they termed RLIP76. The deduced 655-amino acid protein is homologous in the central region to proteins bearing a CDC42 (OMIM Ref. No. 116952)/RHO (see OMIM Ref. No. 165390)/RAC (see OMIM Ref. No. RAC1; 602048) GTPase-activating protein (GAP) activity, such as BCR (see OMIM Ref. No. 151410). Sequence analysis predicted that RALBP1 has an N-terminal alpha-helical region, the GAP-like region, the RAL-binding region, and the C-terminal region. Binding analysis showed that RALBP1 interacts with RALA and RALB (OMIM Ref. No. 179551) but with no other GTPase except RAC1. Northern blot analysis detected ubiquitous, low-level expression of RALBP1.

[17862] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17863] Awasthi, S.; Cheng, J.; Singhal, S. S.; Saini, M. K.; Pandya, U.; Pikula, S.; Bandorowicz-Pikula, J.; Singh, S. V.; Zimniak, P.; Awasthi, Y. C. : Novel function of human RLIP76: ATP-dependent transport of glutathione conjugates and doxorubicin. *Biochemistry* 39: 9327–9334, 2000. ; and

[17864] Jullien-Flores, V.; Dorseuil, O.; Romero, R.; Letourneur, F.; Saragosti, S.; Berger, R.; Tavitian, A.; Gacon, G.; Camonis, J. H. : Bridging Ral GTPase to Rho pathways: RLIP76, a Ral ef.

[17865] Further studies establishing the function and utilities of RALBP1 are found in John Hopkins OMIM database record ID 605801, and in cited publications numbered 737–738 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CSR1 (Accession NM\_016240) is another VGAM345 host target gene. CSR1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

CSR1 BINDING SITE, designated SEQ ID:18356, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17866] Another function of VGAM345 is therefore inhibition of CSR1 (Accession NM\_016240). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSR1. KIAA0601 (Accession XM\_031267) is another VGAM345 host target gene. KIAA0601 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0601, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0601 BINDING SITE, designated SEQ ID:31326, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17867] Another function of VGAM345 is therefore inhibition of KIAA0601 (Accession XM\_031267). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0601. KIAA1505 (Accession XM\_168469) is another VGAM345 host target gene. KIAA1505 BINDING SITE is

HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1505, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1505 BINDING SITE, designated SEQ ID:45193, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17868] Another function of VGAM345 is therefore inhibition of KIAA1505 (Accession XM\_168469). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1505. MR (Accession NM\_031212) is another VGAM345 host target gene. MR BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MR BINDING SITE, designated SEQ ID:25256, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17869] Another function of VGAM345 is therefore inhibition of

MR (Accession NM\_031212). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MR. PTK6 Protein Tyrosine Kinase 6 (PTK6, Accession NM\_005975) is another VGAM345 host target gene. PTK6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PTK6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTK6 BINDING SITE, designated SEQ ID:12596, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17870] Another function of VGAM345 is therefore inhibition of PTK6 Protein Tyrosine Kinase 6 (PTK6, Accession NM\_005975). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTK6. Serine Palmitoyltransferase, Long Chain Base Subunit 2 (SPTLC2, Accession NM\_004863) is another VGAM345 host target gene. SPTLC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPTLC2, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPTLC2 BINDING SITE, designated SEQ ID:11272, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17871] Another function of VGAM345 is therefore inhibition of Serine Palmitoyltransferase, Long Chain Base Subunit 2 (SPTLC2, Accession NM\_004863). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPTLC2. UBX Domain Containing 2 (UBXD2, Accession XM\_043196) is another VGAM345 host target gene. UBXD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBXD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBXD2 BINDING SITE, designated SEQ ID:33912, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17872] Another function of VGAM345 is therefore inhibition of UBX Domain Containing 2 (UBXD2, Accession



XM\_043196). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBXD2. LOC112868 (Accession XM\_053402) is another VGAM345 host target gene. LOC112868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC112868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112868 BINDING SITE, designated SEQ ID:36075, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17873] Another function of VGAM345 is therefore inhibition of LOC112868 (Accession XM\_053402). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112868. LOC256176 (Accession XM\_172889) is another VGAM345 host target gene. LOC256176 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256176, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC256176 BINDING SITE, designated SEQ ID:46169, to the nucleotide sequence of VGAM345 RNA, herein designated VGAM RNA, also designated SEQ ID:3056.

[17874] Another function of VGAM345 is therefore inhibition of LOC256176 (Accession XM\_172889). Accordingly, utilities of VGAM345 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256176. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 346 (VGAM346) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17875] VGAM346 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM346 was detected is described hereinabove with reference to Figs. 1–8.

[17876] VGAM346 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Black Beetle Virus. VGAM346 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[17877] VGAM346 gene encodes a VGAM346 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM346 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM346 precursor RNA is designated SEQ ID:332, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:332 is located at position 1124 relative to the genome of Black Beetle Virus.

[17878] VGAM346 precursor RNA folds onto itself, forming VGAM346 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17879] An enzyme complex designated DICER COMPLEX, `dices` the VGAM346 folded precursor RNA into VGAM346 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM346 RNA is designated SEQ ID:3057, and is provided hereinbelow with reference to the sequence listing part.

[17880] VGAM346 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM346 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM346 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17881] VGAM346 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM346 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM346 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM346 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM346 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17882] The complementary binding of VGAM346 RNA, herein designated VGAM RNA, to host target binding sites on VGAM346 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM346 host target RNA into VGAM346 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17883] It is appreciated that VGAM346 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM346 host target genes. The mRNA of each one of this plurality of VGAM346 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM346 RNA, herein designated VGAM RNA, and which when bound by VGAM346 RNA causes inhibition of translation of respective one or more VGAM346 host target proteins.

[17884] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM346 gene, herein designated VGAM GENE, on one or more VGAM346 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17885] It is yet further appreciated that a function of VGAM346 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of viral infection by Black Beetle Virus. Specific functions, and accordingly utilities, of VGAM346 correlate with, and may be deduced from, the identity of the host target genes which VGAM346 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[17886] Nucleotide sequences of the VGAM346 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM346 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM346 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM346 are further described hereinbelow with reference to Table 1.

[17887] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM346 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM346 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17888] As mentioned hereinabove with reference to Fig. 1, a function of VGAM346 gene, herein designated VGAM is inhibition of expression of VGAM346 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM346 correlate with, and may be deduced from, the identity of the target genes which VGAM346 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17889] Myosin ID (MYO1D, Accession XM\_050041) is a VGAM346 host target gene. MYO1D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYO1D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYO1D BINDING SITE, designated SEQ ID:35548, to the nucleotide sequence of VGAM346 RNA, herein designated VGAM RNA, also designated SEQ ID:3057.



[17890] A function of VGAM346 is therefore inhibition of Myosin ID (MYO1D, Accession XM\_050041), a gene which is an unconventional myosin. Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYO1D. The function of MYO1D and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM126. Osteoglycin (osteoinductive factor, mimecan) (OGN, Accession NM\_024416) is another VGAM346 host target gene. OGN BINDING SITE1 through OGN BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by OGN, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OGN BINDING SITE1 through OGN BINDING SITE3, designated SEQ ID:23655, SEQ ID:26899 and SEQ ID:15275 respectively, to the nucleotide sequence of VGAM346 RNA, herein designated VGAM RNA, also designated SEQ ID:3057.

[17891] Another function of VGAM346 is therefore inhibition of Osteoglycin (osteoinductive factor, mimecan) (OGN, Accession NM\_024416), a gene which induces ectopic bone

formation in conjunction with transforming growth factor beta. Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OGN. The function of OGN has been established by previous studies. Bovine osteoinductive factor (OIF) induces ectopic bone formation in conjunction with TGFB1 (OMIM Ref. No. 190180) or TGFB2 (OMIM Ref. No. 190220) (Bentz et al., 1989). Using primers based on the sequence of purified bovine OIF, Madisen et al. (1990) isolated a human OIF cDNA clone by RT-PCR of osteosarcoma cell mRNA. The human gene encodes a predicted 298-amino acid precursor protein that is processed into a 103-amino acid mature protein with 96% identity to the bovine protein. On Northern blots, 3 OIF mRNAs are found exclusively in 2 human osteosarcoma cell lines. By FISH, Tasheva et al. (2000) mapped the mimecan gene to 9q22. Pellegata et al. (2000) cloned the human OGN gene and mapped it to a region approximately 1.1 Mb telomeric of WI-532 and approximately 700 kb centromeric of D9S197 in 9q22.31.

[17892] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [17893] Madisen, L.; Neubauer, M.; Plowman, G.; Rosen, D.; Segarini, P.; Dasch, J.; Thompson, A.; Ziman, J.; Bentz, H.; Purchio, A. F. : Molecular cloning of a novel bone-forming compound: osteoinductive factor. DNA Cell Biol. 9: 303–309, 1990. ; and
- [17894] Pellegata, N. S.; Dieguez–Lucena, J. L.; Joensuu, T.; Lau, S.; Montgomery, K. T.; Krahe, R.; Kivela, T.; Kucherlapati, R.; Forsius, H.; de la Chapelle, A. : Mutations in KERA, encoding.
- [17895] Further studies establishing the function and utilities of OGN are found in John Hopkins OMIM database record ID 602383, and in cited publications numbered 5605–5606, 340 and 5861 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ30058 (Accession NM\_144967) is another VGAM346 host target gene. FLJ30058 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ30058, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ30058 BINDING SITE, designated SEQ ID:29581, to the nucleotide sequence of VGAM346 RNA, herein designated VGAM

RNA, also designated SEQ ID:3057.

[17896] Another function of VGAM346 is therefore inhibition of FLJ30058 (Accession NM\_144967). Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ30058. KIAA0903 (Accession XM\_049251) is another VGAM346 host target gene. KIAA0903 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0903, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0903 BINDING SITE, designated SEQ ID:35370, to the nucleotide sequence of VGAM346 RNA, herein designated VGAM RNA, also designated SEQ ID:3057.

[17897] Another function of VGAM346 is therefore inhibition of KIAA0903 (Accession XM\_049251). Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0903. MNAB (Accession NM\_018835) is another VGAM346 host target gene. MNAB BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MNAB, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MNAB BINDING SITE, designated SEQ ID:20822, to the nucleotide sequence of VGAM346 RNA, herein designated VGAM RNA, also designated SEQ ID:3057.

[17898] Another function of VGAM346 is therefore inhibition of MNAB (Accession NM\_018835). Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MNAB. SCYD1 (Accession XM\_165650) is another VGAM346 host target gene. SCYD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCYD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCYD1 BINDING SITE, designated SEQ ID:43714, to the nucleotide sequence of VGAM346 RNA, herein designated VGAM RNA, also designated SEQ ID:3057.

[17899] Another function of VGAM346 is therefore inhibition of SCYD1 (Accession XM\_165650). Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with SCYD1. LOC146445 (Accession XM\_096999) is another VGAM346 host target gene. LOC146445 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146445, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146445 BINDING SITE, designated SEQ ID:40700, to the nucleotide sequence of VGAM346 RNA, herein designated VGAM RNA, also designated SEQ ID:3057.

[17900] Another function of VGAM346 is therefore inhibition of LOC146445 (Accession XM\_096999). Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146445. LOC221103 (Accession XM\_167758) is another VGAM346 host target gene. LOC221103 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221103 BINDING SITE, designated SEQ ID:44780, to

the nucleotide sequence of VGAM346 RNA, herein designated VGAM RNA, also designated SEQ ID:3057.

[17901] Another function of VGAM346 is therefore inhibition of LOC221103 (Accession XM\_167758). Accordingly, utilities of VGAM346 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221103. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 347 (VGAM347) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17902] VGAM347 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM347 was detected is described hereinabove with reference to Figs. 1–8.

[17903] VGAM347 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Black Beetle Virus. VGAM347 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[17904] VGAM347 gene encodes a VGAM347 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM347 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM347 precursor RNA is designated SEQ ID:333, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:333 is located at position 1731 relative to the genome of Black Beetle Virus.

[17905] VGAM347 precursor RNA folds onto itself, forming VGAM347 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17906] An enzyme complex designated DICER COMPLEX, `dices` the VGAM347 folded precursor RNA into VGAM347 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short



~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 48%) nucleotide sequence of VGAM347 RNA is designated SEQ ID:3058, and is provided hereinbelow with reference to the sequence listing part.

[17907] VGAM347 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM347 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM347 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[17908] VGAM347 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM347 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM347 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM347 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM347 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17909] The complementary binding of VGAM347 RNA, herein designated VGAM RNA, to host target binding sites on VGAM347 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM347 host target RNA into VGAM347 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17910] It is appreciated that VGAM347 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM347 host target genes. The mRNA of each one of this plurality of VGAM347 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM347 RNA, herein designated VGAM RNA, and which when bound by VGAM347 RNA causes inhibition of translation of respective one or more VGAM347 host target proteins.

[17911] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM347 gene, herein designated VGAM GENE, on one or more VGAM347 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[17912] It is yet further appreciated that a function of VGAM347 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of viral infection by Black Beetle Virus. Specific functions, and accordingly utilities, of VGAM347 correlate with, and may be deduced from, the identity of the host target genes which VGAM347 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[17913] Nucleotide sequences of the VGAM347 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM347 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM347 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM347 are further described hereinbelow with reference to Table 1.

[17914] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM347 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM347 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17915] As mentioned hereinabove with reference to Fig. 1, a function of VGAM347 gene, herein designated VGAM is inhibition of expression of VGAM347 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM347 correlate with, and may be deduced from, the identity of the target genes which VGAM347 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17916] Protein Tyrosine Phosphatase, Non-receptor Type 2 (PTPN2, Accession NM\_002828) is a VGAM347 host target gene. PTPN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTPN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPN2 BINDING SITE, designated SEQ ID:8705, to the nucleotide sequence of VGAM347 RNA, herein designated VGAM RNA, also designated SEQ ID:3058.

[17917] A function of VGAM347 is therefore inhibition of Protein

Tyrosine Phosphatase, Non-receptor Type 2 (PTPN2, Accession NM\_002828). Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPN2. Chromosome 20 Open Reading Frame 108 (C20orf108, Accession NM\_080821) is another VGAM347 host target gene.

C20orf108 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf108, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf108 BINDING SITE, designated SEQ ID:28081, to the nucleotide sequence of VGAM347 RNA, herein designated VGAM RNA, also designated SEQ ID:3058.

[17918] Another function of VGAM347 is therefore inhibition of Chromosome 20 Open Reading Frame 108 (C20orf108, Accession NM\_080821). Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf108. KIAA0884 (Accession XM\_046660) is another VGAM347 host target gene. KIAA0884 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by KIAA0884, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0884 BINDING SITE, designated SEQ ID:34773, to the nucleotide sequence of VGAM347 RNA, herein designated VGAM RNA, also designated SEQ ID:3058.

[17919] Another function of VGAM347 is therefore inhibition of KIAA0884 (Accession XM\_046660). Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0884. Protein Phosphatase 1, Regulatory (inhibitor) Subunit 16B (PPP1R16B, Accession XM\_028840) is another VGAM347 host target gene. PPP1R16B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1R16B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R16B BINDING SITE, designated SEQ ID:30765, to the nucleotide sequence of VGAM347 RNA, herein designated VGAM RNA, also designated SEQ ID:3058.

[17920] Another function of VGAM347 is therefore inhibition of

Protein Phosphatase 1, Regulatory (inhibitor) Subunit 16B (PPP1R16B, Accession XM\_028840). Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R16B. LOC144100 (Accession XM\_084732) is another VGAM347 host target gene. LOC144100 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144100, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144100 BINDING SITE, designated SEQ ID:37676, to the nucleotide sequence of VGAM347 RNA, herein designated VGAM RNA, also designated SEQ ID:3058.

[17921] Another function of VGAM347 is therefore inhibition of LOC144100 (Accession XM\_084732). Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144100. LOC145138 (Accession XM\_096724) is another VGAM347 host target gene. LOC145138 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145138, corresponding to a HOST TARGET binding site such as BIND-



ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145138 BINDING SITE, designated SEQ ID:40503, to the nucleotide sequence of VGAM347 RNA, herein designated VGAM RNA, also designated SEQ ID:3058.

[17922] Another function of VGAM347 is therefore inhibition of LOC145138 (Accession XM\_096724). Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145138. LOC151234 (Accession XM\_087136) is another VGAM347 host target gene. LOC151234 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151234, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151234 BINDING SITE, designated SEQ ID:39079, to the nucleotide sequence of VGAM347 RNA, herein designated VGAM RNA, also designated SEQ ID:3058.

[17923] Another function of VGAM347 is therefore inhibition of LOC151234 (Accession XM\_087136). Accordingly, utilities of VGAM347 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC151234. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 348 (VGAM348) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17924] VGAM348 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM348 was detected is described hereinabove with reference to Figs. 1–8.

[17925] VGAM348 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Enterovirus C. VGAM348 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[17926] VGAM348 gene encodes a VGAM348 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM348 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM348 precursor RNA is designated SEQ ID:334, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:334 is located at position 5074 relative to the genome of Human Enterovirus C.

[17927] VGAM348 precursor RNA folds onto itself, forming VGAM348 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17928] An enzyme complex designated DICER COMPLEX, `dices` the VGAM348 folded precursor RNA into VGAM348 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM348 RNA is designated SEQ ID:3059, and is provided hereinbelow with reference to the sequence listing part.

[17929] VGAM348 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM348 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM348 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17930] VGAM348 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM348 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM348 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM348 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM348 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[17931] The complementary binding of VGAM348 RNA, herein designated VGAM RNA, to host target binding sites on VGAM348 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM348 host target RNA into VGAM348 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17932] It is appreciated that VGAM348 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM348 host target genes. The mRNA of each one of this plurality of VGAM348 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM348 RNA, herein designated VGAM RNA, and which when bound by VGAM348 RNA causes in-

hibition of translation of respective one or more VGAM348 host target proteins.

[17933] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM348 gene, herein designated VGAM GENE, on one or more VGAM348 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17934] It is yet further appreciated that a function of VGAM348 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM348 include diagnosis, prevention and

treatment of viral infection by Human Enterovirus C. Specific functions, and accordingly utilities, of VGAM348 correlate with, and may be deduced from, the identity of the host target genes which VGAM348 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [17935] Nucleotide sequences of the VGAM348 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM348 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM348 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM348 are further described hereinbelow with reference to Table 1.
- [17936] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM348 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM348 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [17937] As mentioned hereinabove with reference to Fig. 1, a function of VGAM348 gene, herein designated VGAM is inhibition of expression of VGAM348 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM348 correlate with, and may be deduced from, the identity of the target genes which VGAM348 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17938] KIAA0828 (Accession XM\_088105) is a VGAM348 host target gene. KIAA0828 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0828, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0828 BINDING SITE, designated SEQ ID:39517, to the nucleotide sequence of VGAM348 RNA, herein designated VGAM RNA, also designated SEQ ID:3059.

[17939] A function of VGAM348 is therefore inhibition of KIAA0828 (Accession XM\_088105). Accordingly, utilities of VGAM348 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0828. LOC157909 (Accession XM\_088419) is another VGAM348 host target gene. LOC157909 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157909, corresponding



to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157909 BINDING SITE, designated SEQ ID:39678, to the nucleotide sequence of VGAM348 RNA, herein designated VGAM RNA, also designated SEQ ID:3059.

[17940] Another function of VGAM348 is therefore inhibition of LOC157909 (Accession XM\_088419). Accordingly, utilities of VGAM348 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157909. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 349 (VGAM349) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17941] VGAM349 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM349 was detected is described hereinabove with reference to Figs. 1–8.

[17942] VGAM349 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Enterovirus C.

VGAM349 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[17943] VGAM349 gene encodes a VGAM349 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM349 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM349 precursor RNA is designated SEQ ID:335, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:335 is located at position 7103 relative to the genome of Human Enterovirus C.

[17944] VGAM349 precursor RNA folds onto itself, forming VGAM349 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17945] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM349 folded precursor RNA into VGAM349 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 63%) nucleotide sequence of VGAM349 RNA is designated SEQ ID:3060, and is provided hereinbelow with reference to the sequence listing part.

[17946] VGAM349 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM349 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM349 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17947] VGAM349 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM349 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM349 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM349 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM349 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17948] The complementary binding of VGAM349 RNA, herein designated VGAM RNA, to host target binding sites on VGAM349 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM349 host target RNA into VGAM349 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17949] It is appreciated that VGAM349 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM349 host target genes. The mRNA of each one of this plurality of VGAM349 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM349 RNA, herein designated VGAM RNA, and which when bound by VGAM349 RNA causes inhibition of translation of respective one or more VGAM349 host target proteins.

[17950] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM349 gene, herein designated VGAM GENE, on one or more VGAM349 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[17951] It is yet further appreciated that a function of VGAM349 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of viral infection by Human Enterovirus C. Specific functions, and accordingly utilities, of VGAM349 correlate with, and may be deduced from, the identity of the host target genes which VGAM349 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[17952] Nucleotide sequences of the VGAM349 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM349 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM349 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM349 are further described hereinbelow with reference to Table 1.

- [17953] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM349 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM349 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [17954] As mentioned hereinabove with reference to Fig. 1, a function of VGAM349 gene, herein designated VGAM is inhibition of expression of VGAM349 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM349 correlate with, and may be deduced from, the identity of the target genes which VGAM349 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [17955] Isocitrate Dehydrogenase 3 (NAD<sup>+</sup>) Alpha (IDH3A, Accession NM\_005530) is a VGAM349 host target gene. IDH3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IDH3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IDH3A BINDING SITE, designated SEQ ID:12053, to the

nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17956] A function of VGAM349 is therefore inhibition of Isocitrate Dehydrogenase 3 (NAD<sup>+</sup>) Alpha (IDH3A, Accession NM\_005530), a gene which decarboxylates isocitrate into alpha-ketoglutarate in the TCA cycle. Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IDH3A. The function of IDH3A has been established by previous studies. Isocitrate dehydrogenases (EC 1.1.1.4.1 and EC 1.1.1.42) catalyze the oxidative decarboxylation of isocitrate into alpha-ketoglutarate. Thus, they are key enzymes in the tricarboxylic acid (TCA) cycle. In mammalian tissues, 3 kinds of isoenzymes exist, cytosolic NADP(+)-specific IDH (OMIM Ref. No. 147700), mitochondrial NADP(+)-specific IDH (OMIM Ref. No. 147650), and mitochondrial NAD(+)-specific IDH (IDH3). Among the mammalian IDH isoenzymes, IDH3 is thought to play a major role in isocitrate decarboxylation in the TCA cycle, since its activity is regulated by numerous allosteric regulators. IDH3, purified to homogeneity from pig heart, is a heterotetramer of the 2-alpha, 1-beta, and 1-gamma subunits, while NADP(+)-specific IDH found in either mi-



tochondria or cytosol is a homodimer. Kim et al. (1995) characterized the cDNA clone for the alpha subunit (IDH3A), which encodes a mature protein with 339 amino acids (36,640 Da). Kim et al. (1995) had found that the human IDH3A sequence showed 44 and 30% amino acid identity to the monkey IDH3G (OMIM Ref. No. 602017) and bovine IDH2 (OMIM Ref. No. 147650) genes, respectively. Preliminary data using fluorescence in situ hybridization (FISH) supported the assignment to 15q26.1. By FISH, Huh et al. (1996) mapped the IDH3A gene to 15q25.1–q25.2

[17957] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17958] Huh, T.–L.; Kim, Y.–O.; Oh, I.–U.; Song, B. J.; Inazawa, J. : Assignment of the human mitochondrial NAD(+)-specific isocitrate dehydrogenase alpha subunit (IDH3A) gene to 15q25.1–q25.2 by in situ hybridization. Genomics 31: 295–296, 1996. ; and

[17959] Kim, Y.–O.; Oh, I.–U.; Park, H.–S.; Jeng, J.; Song, B. J.; Huh, T.–L. : Characterization of a cDNA clone for human NAD(+)-specific isocitrate dehydrogenase alpha-subunit and structural c.

[17960] Further studies establishing the function and utilities of IDH3A are found in John Hopkins OMIM database record ID 601149, and in cited publications numbered 7539–7540 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Lipin 1 (LPIN1, Accession XM\_041136) is another VGAM349 host target gene. LPIN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LPIN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LPIN1 BINDING SITE, designated SEQ ID:33470, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17961] Another function of VGAM349 is therefore inhibition of Lipin 1 (LPIN1, Accession XM\_041136), a gene which is involved in adipocyte differentiation (by similarity). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LPIN1. The function of LPIN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove

with reference to VGAM35.LIM Domain Containing Preferred Translocation Partner In Lipoma (LPP, Accession NM\_005578) is another VGAM349 host target gene. LPP BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LPP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LPP BINDING SITE, designated SEQ ID:12108, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17962] Another function of VGAM349 is therefore inhibition of LIM Domain Containing Preferred Translocation Partner In Lipoma (LPP, Accession NM\_005578). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LPP. Retinoschisis (X-linked, juvenile) 1 (RS1, Accession NM\_000330) is another VGAM349 host target gene. RS1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

RS1 BINDING SITE, designated SEQ ID:5879, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17963] Another function of VGAM349 is therefore inhibition of Retinoschisis (X-linked, juvenile) 1 (RS1, Accession NM\_000330). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RS1. Retinoid X Receptor, Alpha (RXRA, Accession NM\_002957) is another VGAM349 host target gene. RXRA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RXRA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RXRA BINDING SITE, designated SEQ ID:8873, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17964] Another function of VGAM349 is therefore inhibition of Retinoid X Receptor, Alpha (RXRA, Accession NM\_002957), a gene which activates genes required for vitamin A metabolism, binds 9-cis retinoic acid. Accordingly, utilities of VGAM349 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with RXRA. The function of RXRA has been established by previous studies. Retinoic acid has been implicated in many aspects of vertebrate development and homeostasis. Its effects are mediated by specific nuclear receptor proteins that are members of the steroid and thyroid hormone receptor superfamily of transcriptional regulators. In addition to the high affinity retinoic acid receptors termed alpha (RARA; 180240), beta (RARB; 180220), and gamma (RARG; 180190), Mangelsdorf et al. (1990, 1991) identified a distinct nuclear receptor referred to as retinoid X receptor alpha. This receptor differs from the other 3 RARs within the ligand-binding domain and is incapable of high affinity binding of retinoic acid itself. The retinoic acid, thyroid hormone, and vitamin D receptors, as well as the retinoid X receptor, activate transcription from response elements containing 2 or more degenerate copies of the consensus motif AGGTCA. Heyman et al. (1992) presented evidence that 9-cis retinoic acid is a high affinity ligand for RXRA. McNamara et al. (2001) reported a hormone-dependent interaction of the nuclear receptors RARA and RXRA with CLOCK (OMIM Ref. No. 601851) and MOP4 (OMIM Ref. No. 603347). They found that these in-

teractions negatively regulate CLOCK–BMAL1 (OMIM Ref. No. 602550) and MOP4–BMAL1 heterodimer–mediated transcriptional activation of clock gene expression in vascular cells. MOP4 exhibited a robust rhythm in the vasculature, and retinoic acid could phase shift PER2 (OMIM Ref. No. 603426) mRNA rhythmicity in vivo and in serum-induced smooth muscle cells in vitro, providing a molecular mechanism for hormonal control of clock gene expression. McNamara et al. (2001) proposed that circadian or periodic availability of nuclear hormones may play a critical role in resetting a peripheral vascular clock. Using RFLVs in interspecific backcross mice, Hoopes et al. (1992) mapped mouse genomic loci *Rxra*, *Rxrb*, and *Rxrg* to chromosome 2 near the centromere, to the H-2 region of chromosome 17, and to distal chromosome 1 in tight linkage with the *Pbx* (OMIM Ref. No. 176310) gene, respectively. Jones et al. (1993) mapped the *RXRA* gene to chromosome 9 by using PCR on a panel of somatic cell hybrids. A cosmid clone was isolated using the *RXRA* PCR product, and this was used to localize the gene further by fluorescence in situ hybridization to 9q34, distal to the dopamine beta-hydroxylase gene (*DBH*; 223360). The mapping position was confirmed by PCR on a panel of

translocation hybrids. By pairwise hybridization of an RXRA cosmid and reference markers in fluorescence in situ hybridization, Almasan et al. (1994) refined the localization to 9q34.3. Fusion of PML (OMIM Ref. No. 102578) and TIF1A (OMIM Ref. No. 603406) to RARA and BRAF (OMIM Ref. No. 164757), respectively, results in the production of PML-RAR-alpha and TIF1-alpha-B-RAF (T18) oncoproteins. Zhong et al. (1999) showed that PML, TIF1-alpha, and RXR-alpha/RAR-alpha function together in a retinoic acid-dependent transcription complex. Zhong et al. (1999) found that PML acts as a ligand-dependent coactivator of RXR-alpha/RARA-alpha. T18, similar to PML-RAR-alpha, disrupts the retinoic acid-dependent activity of this complex in a dominant-negative manner, resulting in a growth advantage. PML-RAR-alpha was the first example of an oncoprotein generated by the fusion of 2 molecules participating in the same pathway, specifically the fusion of a transcription factor to one of its own cofactors. Since the PML and RAR-alpha pathways converge at the transcriptional level, there is no need for a double-dominant-negative product to explain the pathogenesis of acute promyelocytic leukemia, or APL. Germain et al. (2002) showed that RXR can bind ligand and recruit

coactivators as a heterodimer with apo-retinoic acid receptor (apo-RAR). However, in the usual cellular environment corepressors do not dissociate and they prohibit coactivator access because coregulator binding is mutually exclusive. Animal model experiments lend further support to the function of RXRA. Li et al. (2000) developed an efficient technique to create spatiotemporally controlled somatic mutations of the Rxr-alpha gene in the mouse. Li et al. (2000) used tamoxifen-inducible Cre-ER(T) recombinases to ablate RXR-alpha selectively in adult mouse keratinocytes. In 6 to 7 weeks after the first tamoxifen treatment, alopecia developed in the ventral region of pro-mutant mice. At 12 to 16 weeks after treatment, large regions of ventral skin and smaller regions of dorsal skin were hairless. Cysts became visible under the skin surface and these enlarged and spread all over the body with time. At 16 weeks after treatment, hairless regions showed hair follicle degeneration, resulting in utriculi and dermal cysts. Keratin 6 (OMIM Ref. No. 148041), which is usually expressed only in hair follicle outer root sheath, was also expressed in hyperproliferative interfollicular epidermis, indicating abnormal keratinocyte terminal differentiation. All abnormalities were less severe,



and/or appeared later, in males than in females. Li et al. (2000) found that RXR-beta (OMIM Ref. No. 180246) expression in adult skin is several-fold higher in males than in females. Study of tamoxifen-treated RXR-alpha/RXR-beta compound mutants demonstrated that RXR-beta can partially compensate for a loss of RXR-alpha function. Also, in accordance with a larger amount of RXR-beta in adult male skin, the functional redundancy was more pronounced in males than in females, as RXR-alpha/beta double mutant males and females were similarly affected, unlike the single mutants. De Urquiza et al. (2000) identified docosahexaenoic acid (DHA), a long-chain polyunsaturated fatty acid that is highly enriched in the adult mammalian brain, as the natural ligand for the retinoic X receptor in mouse brain. Claudel et al. (2001) analyzed the effects of activation of RXR and some of its heterodimers in apolipoprotein E -/- mice, a well-established animal model of atherosclerosis. An RXR agonist drastically reduced the development of atherosclerosis. In addition, a ligand for the peroxisome proliferator-activated receptor PPAR-gamma and a dual agonist of both PPAR-alpha and PPAR-gamma had moderate inhibitory effects. Both RXR and LXR agonists induced ATP-binding

cassette protein-1 (ABC1) expression and stimulated ABC1-mediated cholesterol efflux from macrophages from wildtype, but not from LXRA or LXR $\beta$  (OMIM Ref. No. 600380), double -/- mice. Hence, activation of ABC1-mediated cholesterol efflux by the RXR/LXR heterodimer may contribute to the beneficial effects of rexinoids on atherosclerosis and warrant further evaluation of RXR/LXR agonists in prevention and treatment of atherosclerosis.

[17965] It is appreciated that the abovementioned animal model for RXRA is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[17966] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17967] Claudel, T.; Leibowitz, M. D.; Fievet, C.; Tailleux, A.; Wagner, B.; Repa, J. J.; Torpier, G.; Lobaccaro, J.-M.; Paterniti, J. R.; Mangelsdorf, D. J.; Heyman, R. A.; Auwerx, J. : Reduction of atherosclerosis in apolipoprotein E knockout mice by activation of the retinoid X receptor. Proc. Nat. Acad. Sci. 98: 2610-2615, 2001. ; and

[17968] Germain, P.; Iyer, J.; Zechel, C.; Gronemeyer, H. : Co-

regulator recruitment and the mechanism of retinoic acid receptor synergy. *Nature* 415: 187–192, 2002.

[17969] Further studies establishing the function and utilities of RXRA are found in John Hopkins OMIM database record ID 180245, and in cited publications numbered 2726–2728, 5934–5935, 2724, 5936–5943, 2725, 5944–5945, 594 and 11302 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 6 Open Reading Frame 32 (C6orf32, Accession NM\_015864) is another VGAM349 host target gene. C6orf32 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C6orf32, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C6orf32 BINDING SITE, designated SEQ ID:17994, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17970] Another function of VGAM349 is therefore inhibition of Chromosome 6 Open Reading Frame 32 (C6orf32, Accession NM\_015864). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with C6orf32. FLJ12221 (Accession XM\_031342) is another VGAM349 host target gene. FLJ12221 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12221, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12221 BINDING SITE, designated SEQ ID:31346, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17971] Another function of VGAM349 is therefore inhibition of FLJ12221 (Accession XM\_031342). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12221. FLJ20986 (Accession NM\_024524) is another VGAM349 host target gene. FLJ20986 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20986, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20986 BINDING SITE, designated SEQ ID:23731, to the nucleotide sequence of

VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17972] Another function of VGAM349 is therefore inhibition of FLJ20986 (Accession NM\_024524). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20986. HUMAGCGB (Accession NM\_013286) is another VGAM349 host target gene. HUMAGCGB BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HUMAGCGB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HUMAGCGB BINDING SITE, designated SEQ ID:14957, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17973] Another function of VGAM349 is therefore inhibition of HUMAGCGB (Accession NM\_013286). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUMAGCGB. KIAA0831 (Accession NM\_014924) is another VGAM349 host target gene. KIAA0831 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA0831, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0831 BINDING SITE, designated SEQ ID:17211, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17974] Another function of VGAM349 is therefore inhibition of KIAA0831 (Accession NM\_014924). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0831. LOC129607 (Accession XM\_059368) is another VGAM349 host target gene. LOC129607 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC129607, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC129607 BINDING SITE, designated SEQ ID:36973, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17975] Another function of VGAM349 is therefore inhibition of LOC129607 (Accession XM\_059368). Accordingly, utilities

of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129607. LOC150819 (Accession XM\_097954) is another VGAM349 host target gene. LOC150819 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150819, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150819 BINDING SITE, designated SEQ ID:41246, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17976] Another function of VGAM349 is therefore inhibition of LOC150819 (Accession XM\_097954). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150819. LOC152905 (Accession XM\_017966) is another VGAM349 host target gene. LOC152905 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152905, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC152905 BINDING SITE, designated SEQ ID:30334, to the nucleotide sequence of VGAM349 RNA, herein designated VGAM RNA, also designated SEQ ID:3060.

[17977] Another function of VGAM349 is therefore inhibition of LOC152905 (Accession XM\_017966). Accordingly, utilities of VGAM349 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152905. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 350 (VGAM350) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[17978] VGAM350 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM350 was detected is described hereinabove with reference to Figs. 1–8.

[17979] VGAM350 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM350 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.



[17980] VGAM350 gene encodes a VGAM350 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM350 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM350 precursor RNA is designated SEQ ID:336, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:336 is located at position 2089 relative to the genome of Avian Infectious Bronchitis Virus.

[17981] VGAM350 precursor RNA folds onto itself, forming VGAM350 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[17982] An enzyme complex designated DICER COMPLEX, `dices` the VGAM350 folded precursor RNA into VGAM350 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM350 RNA is designated SEQ ID:3061, and is provided hereinbelow with reference to the sequence listing part.

[17983] VGAM350 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM350 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM350 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[17984] VGAM350 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM350 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM350 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM350 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM350 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[17985] The complementary binding of VGAM350 RNA, herein designated VGAM RNA, to host target binding sites on VGAM350 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM350 host target RNA into VGAM350 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[17986] It is appreciated that VGAM350 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM350 host target genes. The mRNA of each one of this plurality of VGAM350 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM350 RNA, herein designated VGAM RNA, and which when bound by VGAM350 RNA causes inhibition of translation of respective one or more VGAM350 host target proteins.

[17987] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM350 gene, herein designated VGAM GENE, on one or more VGAM350 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[17988] It is yet further appreciated that a function of VGAM350 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM350 correlate with, and may be deduced from, the identity of the host target genes which VGAM350 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[17989] Nucleotide sequences of the VGAM350 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM350 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM350 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM350 are further described hereinbelow with reference to Table 1.

[17990] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM350 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM350 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[17991] As mentioned hereinabove with reference to Fig. 1, a function of VGAM350 gene, herein designated VGAM is inhibition of expression of VGAM350 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM350 correlate with, and may be deduced from, the identity of the target genes which VGAM350 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[17992] Coagulation Factor II (thrombin) Receptor-like 3 (F2RL3, Accession NM\_003950) is a VGAM350 host target gene. F2RL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by F2RL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F2RL3 BINDING SITE, designated SEQ ID:10078, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[17993] A function of VGAM350 is therefore inhibition of Coagulation Factor II (thrombin) Receptor-like 3 (F2RL3, Accession NM\_003950), a gene which Protease-activated receptor 4; G protein-coupled receptor that increases phosphoinositide hydrolysis. Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F2RL3. The function of F2RL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM193. Sorting Nexin 6 (SNX6, Accession NM\_021249) is another VGAM350 host target gene. SNX6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SNX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNX6 BINDING SITE, designated SEQ ID:22216, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[17994] Another function of VGAM350 is therefore inhibition of Sorting Nexin 6 (SNX6, Accession NM\_021249). Accordingly, utilities of VGAM350 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with SNX6. TIA1 Cytotoxic Granule-associated RNA Binding Protein-like 1 (TIAL1, Accession NM\_022333) is another VGAM350 host target gene. TIAL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIAL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIAL1 BINDING SITE, designated SEQ ID:22740, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[17995] Another function of VGAM350 is therefore inhibition of TIA1 Cytotoxic Granule-associated RNA Binding Protein-like 1 (TIAL1, Accession NM\_022333), a gene which possesses nucleolytic activity against cytotoxic lymphocyte target cells. Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIAL1. The function of TIAL1 has been established by previous studies. Cytotoxic lymphocytes can induce target cells to activate apoptosis. Central to this autolytic pathway is the activation of an endogenous endonuclease that degrades target cell DNA.



By screening a human phytohemagglutinin-activated T-cell cDNA library with a TIA1 (OMIM Ref. No. 603518) cDNA, Kawakami et al. (1992) cloned a cDNA encoding TIA1-related protein (TIAR). Both TIAR and TIA1 are members of a family of RNA-binding proteins containing 3 RNA-binding domains and a C-terminal auxiliary domain. Like TIA1, TIAR possesses a lysosome-targeting motif in its C-terminal auxiliary domain, suggesting that TIAR is also a cytotoxic granule-associated protein. The authors demonstrated that TIAR binds specifically to poly(A) homopolymers, fragments DNA in permeabilized target cells, and is expressed in a wide variety of hematopoietic and nonhematopoietic cell types. Using a Southwestern approach to identify proteins capable of binding to the T cluster of the platelet factor-4 (PF4; 173460) promoter, Doi et al. (1997) isolated a human erythroleukemia (HEL) cell cDNA encoding an isoform of TIAL1, which they called TCBP. This deduced 265-amino acid isoform differs from the isoform identified by Kawakami et al. (1992) at the C terminus, where a hydrophobic sequence replaces the lysosome-targeting motif. Doi et al. (1997) demonstrated that TCBP specifically binds to the T cluster and the proximal T-rich region of the PF4 promoter in vitro and that

TCBP reduces gene expression from the PF4 promoter.

TCBP mRNA expression was reduced when HEL cells were induced to differentiate to megakaryocytes.

[17996] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[17997] Kawakami, A.; Tian, Q.; Duan, X.; Streuli, M.; Schlossman, S. F.; Anderson, P. : Identification and functional characterization of a TIA-1-related nucleolysin. Proc. Nat. Acad. Sci. 89: 8681-8685, 1992. ; and

[17998] Doi, T.; Minami, T.; Itoh, M.; Aburatani, H.; Kawabe, Y.; Kodama, T.; Kondo, N.; Satoh, Y.; Asayama, T.; Imanishi, T. : An alternative form of nucleolysin binds to a T-cluster DNA in t.

[17999] Further studies establishing the function and utilities of TIAL1 are found in John Hopkins OMIM database record ID 603413, and in cited publications numbered 5294-5295 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tumor Necrosis Factor (ligand) Superfamily, Member 15 (TNFSF15, Accession NM\_005118) is another VGAM350 host target gene. TNFSF15 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TN-

FSF15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFSF15 BINDING SITE, designated SEQ ID:11597, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18000] Another function of VGAM350 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 15 (TNFSF15, Accession NM\_005118), a gene which acts as an autocrine factor to induce apoptosis in endothelial cells. Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFSF15. The function of TNFSF15 has been established by previous studies. Zhai et al. (1999) found that expression of a recombinant soluble form of VEGF inhibited the growth of colon carcinomas in mice, and the tumors expressing the soluble VEGF had markedly reduced vascularization. Conditioned media from cells expressing soluble VEGF dramatically inhibited proliferation of bovine aortic endothelial cells. Zhai et al. (1999) concluded that VEGF is an angiogenesis inhibitor that functions in part by directly inhibiting endothelial cell

proliferation. Yue et al. (1999) reported that TL1 causes endothelial cell apoptosis via activation of the stress protein kinases SAPK/JNK (see OMIM Ref. No. 601158) and p38 MAPK (see OMIM Ref. No. 600289) and the caspases, primarily caspase-3 (OMIM Ref. No. 600636). By functional analysis, Migone et al. (2002) showed that TL1A, but not TL1, induces nuclear factor kappa-B (NFkB; OMIM Ref. No. 164011) activation in cells expressing DR3. Exposure of T lymphocytes, but not other cells, to TL1A enhanced IL2 receptor-alpha (IL2RA; 147730) and IL2 receptor-beta (IL2RB; 146710) expression on these cells, increased proliferation in response to IL2 (OMIM Ref. No. 147680), and induced secretion of IFNG and granulocyte-macrophage colony-stimulating factor (GMCSF, or CSF2; 138960), but not other cytokines, especially in the presence of anti-CD28 (OMIM Ref. No. 186760) costimulation. Exposure of an erythroleukemic cell line (TF-1), but not activated T cells, to TL1A induced caspase activation and cell death, particularly when protein synthesis was inhibited. Migone et al. (2002) showed that treatment of mice with recombinant TL1A strongly enhanced graft-versus-host reactivity, consistent with DR3 being mainly expressed on activated T cells.

- [18001] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [18002] Yue, T.-L.; Ni, J.; Romanic, A. M.; Gu, J.-L.; Keller, P.; Wang, C.; Kumar, S.; Yu, G.; Hart, T. K.; Wang, X.; Xia, Z.; DeWolf, W. E., Jr.; Feuerstein, G. Z. : TL1, a novel tumor necrosis factor-like cytokine, induces apoptosis in endothelial cells: involvement of activation of stress protein kinases (stress-activated protein kinase and p38 mitogen-activated protein kinase) and caspase-3-like protease. *J. Biol. Chem.* 274: 1479-1486, 1999. ; and
- [18003] Zhai, Y.; Ni, J.; Jiang, G.-W.; Lu, J.; Xing, L.; Lincoln, C.; Carter, K. C.; Janat, F.; Kozak, D.; Xu, S.; Rojas, L.; Aggarwal, B. B.; Ruben, S.; Li, L.-Y.; Gentz, R.; Yu, G.-L. : VEGF.
- [18004] Further studies establishing the function and utilities of TNFSF15 are found in John Hopkins OMIM database record ID 604052, and in cited publications numbered 232 and 8584 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Calneuron 1 (CALN1, Accession NM\_031468) is another VGAM350 host target gene. CALN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CALN1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CALN1 BINDING SITE, designated SEQ ID:25509, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18005] Another function of VGAM350 is therefore inhibition of Calneuron 1 (CALN1, Accession NM\_031468). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CALN1. FLJ11053 (Accession XM\_114194) is another VGAM350 host target gene. FLJ11053 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11053, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11053 BINDING SITE, designated SEQ ID:42775, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18006] Another function of VGAM350 is therefore inhibition of FLJ11053 (Accession XM\_114194). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ11053. FLJ11273 (Accession NM\_018374) is another VGAM350 host target gene. FLJ11273 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11273 BINDING SITE, designated SEQ ID:20391, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18007] Another function of VGAM350 is therefore inhibition of FLJ11273 (Accession NM\_018374). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11273. FLJ12700 (Accession NM\_024910) is another VGAM350 host target gene. FLJ12700 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12700 BINDING SITE, designated SEQ ID:24411, to the nucleotide sequence of

VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18008] Another function of VGAM350 is therefore inhibition of FLJ12700 (Accession NM\_024910). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12700. FLJ21736 (Accession NM\_024922) is another VGAM350 host target gene. FLJ21736 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21736, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21736 BINDING SITE, designated SEQ ID:24456, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18009] Another function of VGAM350 is therefore inhibition of FLJ21736 (Accession NM\_024922). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21736. Golgi Autoantigen, Golgin Subfamily A, 3 (GOLGA3, Accession NM\_005895) is another VGAM350 host target gene. GOLGA3 BINDING SITE is HOST TARGET binding site



found in the 3' untranslated region of mRNA encoded by GOLGA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GOLGA3 BINDING SITE, designated SEQ ID:12513, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18010] Another function of VGAM350 is therefore inhibition of Golgi Autoantigen, Golgin Subfamily A, 3 (GOLGA3, Accession NM\_005895). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GOLGA3. G Protein-coupled Receptor 64 (GPR64, Accession NM\_005756) is another VGAM350 host target gene. GPR64 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR64, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR64 BINDING SITE, designated SEQ ID:12314, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18011] Another function of VGAM350 is therefore inhibition of G Protein-coupled Receptor 64 (GPR64, Accession NM\_005756). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR64. Hemogen (HEMGN, Accession NM\_018437) is another VGAM350 host target gene. HEMGN BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HEMGN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HEMGN BINDING SITE, designated SEQ ID:20498, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18012] Another function of VGAM350 is therefore inhibition of Hemogen (HEMGN, Accession NM\_018437). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HEMGN. KIAA1200 (Accession XM\_031054) is another VGAM350 host target gene. KIAA1200 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1200, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1200 BINDING SITE, designated SEQ ID:31260, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18013] Another function of VGAM350 is therefore inhibition of KIAA1200 (Accession XM\_031054). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1200. KIAA1456 (Accession XM\_040100) is another VGAM350 host target gene. KIAA1456 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1456, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1456 BINDING SITE, designated SEQ ID:33260, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18014] Another function of VGAM350 is therefore inhibition of KIAA1456 (Accession XM\_040100). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1456. KIAA1494 (Accession XM\_043561) is another VGAM350 host target gene. KIAA1494 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1494, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1494 BINDING SITE, designated SEQ ID:33960, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18015] Another function of VGAM350 is therefore inhibition of KIAA1494 (Accession XM\_043561). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1494. KIAA1508 (Accession XM\_030209) is another VGAM350 host target gene. KIAA1508 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1508, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1508 BINDING SITE, designated SEQ ID:30992, to the

nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18016] Another function of VGAM350 is therefore inhibition of KIAA1508 (Accession XM\_030209). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1508. MGC5338 (Accession NM\_024062) is another VGAM350 host target gene. MGC5338 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC5338, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5338 BINDING SITE, designated SEQ ID:23497, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18017] Another function of VGAM350 is therefore inhibition of MGC5338 (Accession NM\_024062). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5338. NIFU (Accession XM\_041081) is another VGAM350 host target gene. NIFU BINDING SITE is HOST TARGET binding site found in the 5' untranslated region

of mRNA encoded by NIFU, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NIFU BINDING SITE, designated SEQ ID:33435, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18018] Another function of VGAM350 is therefore inhibition of NIFU (Accession XM\_041081). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NIFU. PB1 (Accession NM\_018165) is another VGAM350 host target gene. PB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PB1 BINDING SITE, designated SEQ ID:19977, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18019] Another function of VGAM350 is therefore inhibition of PB1 (Accession NM\_018165). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PB1. TA-PP2C (Accession NM\_139283) is another VGAM350 host target gene. TA-PP2C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TA-PP2C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TA-PP2C BINDING SITE, designated SEQ ID:29280, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18020] Another function of VGAM350 is therefore inhibition of TA-PP2C (Accession NM\_139283). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TA-PP2C. LOC128989 (Accession XM\_059310) is another VGAM350 host target gene. LOC128989 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC128989, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC128989 BINDING SITE, designated SEQ ID:36937, to the nucleotide se-

quence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18021] Another function of VGAM350 is therefore inhibition of LOC128989 (Accession XM\_059310). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC128989. LOC150577 (Accession XM\_097918) is another VGAM350 host target gene. LOC150577 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150577, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150577 BINDING SITE, designated SEQ ID:41214, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18022] Another function of VGAM350 is therefore inhibition of LOC150577 (Accession XM\_097918). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150577. LOC256950 (Accession XM\_170922) is another VGAM350 host target gene. LOC256950 BINDING SITE is HOST TARGET binding site found in the 3' un-



translated region of mRNA encoded by LOC256950, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256950 BINDING SITE, designated SEQ ID:45700, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18023] Another function of VGAM350 is therefore inhibition of LOC256950 (Accession XM\_170922). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256950. LOC91263 (Accession XM\_037264) is another VGAM350 host target gene. LOC91263 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91263, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91263 BINDING SITE, designated SEQ ID:32593, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18024] Another function of VGAM350 is therefore inhibition of LOC91263 (Accession XM\_037264). Accordingly, utilities

of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91263. LOC91628 (Accession XM\_039701) is another VGAM350 host target gene. LOC91628 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91628, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91628 BINDING SITE, designated SEQ ID:33161, to the nucleotide sequence of VGAM350 RNA, herein designated VGAM RNA, also designated SEQ ID:3061.

[18025] Another function of VGAM350 is therefore inhibition of LOC91628 (Accession XM\_039701). Accordingly, utilities of VGAM350 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91628. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 351 (VGAM351) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18026] VGAM351 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM351 was detected is described hereinabove with reference to Figs. 1–8.

[18027] VGAM351 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM351 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18028] VGAM351 gene encodes a VGAM351 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM351 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM351 precursor RNA is designated SEQ ID:337, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:337 is located at position 8232 relative to the genome of Avian Infectious Bronchitis Virus.

[18029] VGAM351 precursor RNA folds onto itself, forming VGAM351 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18030] An enzyme complex designated DICER COMPLEX, `dices` the VGAM351 folded precursor RNA into VGAM351 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 55%) nucleotide sequence of VGAM351 RNA is designated SEQ ID:3062, and is provided hereinbelow with reference to the sequence listing part.

[18031] VGAM351 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM351 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM351 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[18032] VGAM351 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM351 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM351 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM351 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM351 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18033] The complementary binding of VGAM351 RNA, herein designated VGAM RNA, to host target binding sites on VGAM351 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM351 host target RNA into VGAM351 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18034] It is appreciated that VGAM351 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM351 host target genes. The mRNA of each one of this plurality of VGAM351 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM351 RNA, herein designated VGAM RNA, and which when bound by VGAM351 RNA causes inhibition of translation of respective one or more VGAM351 host target proteins.

[18035] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM351 gene, herein designated VGAM GENE, on one or more VGAM351 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18036] It is yet further appreciated that a function of VGAM351 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM351 correlate with, and may be deduced from, the identity of the host target genes which VGAM351 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18037] Nucleotide sequences of the VGAM351 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM351 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM351 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM351 are further  
described hereinbelow with reference to Table 1.

[18038] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM351 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM351 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[18039] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM351 gene, herein designated VGAM is  
inhibition of expression of VGAM351 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM351 correlate with, and may be deduced  
from, the identity of the target genes which VGAM351  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[18040] Neuroblastoma RAS Viral (v-ras) Oncogene Homolog  
(NRAS, Accession NM\_002524) is a VGAM351 host target



gene. NRAS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRAS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRAS BINDING SITE, designated SEQ ID:8359, to the nucleotide sequence of VGAM351 RNA, herein designated VGAM RNA, also designated SEQ ID:3062.

[18041] A function of VGAM351 is therefore inhibition of Neuroblastoma RAS Viral (v-ras) Oncogene Homolog (NRAS, Accession NM\_002524), a gene which ras proteins bind gdp/gtp and possess intrinsic gtpase activity. Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRAS. The function of NRAS has been established by previous studies. Hall et al. (1983) cloned an oncogene, which they termed N-RAS, from 2 human sarcoma cell lines, HT1080 and RD, and showed that it is a member of the RAS gene family; that it is encoded by a gene on chromosome 1; and that the same gene is activated in HL60, a promyelocytic leukemia line. Hall et al. (1983) settled on the designation NRAS 'after consultation with Wigler and with Weinberg.' De Martinville et al. (1984) assigned NRAS

to 1p31–cen. By in situ hybridization, Davis et al. (1983) assigned the NRAS gene to the short arm of chromosome 1. A concentration of grains was observed just above the centromere in band 1p13. They commented on the wide dispersion of the oncogenes in the RAS family; each of the 5 mapped to date was on a separate chromosome. Ryan et al. (1983) confirmed assignment of HRAS (OMIM Ref. No. 190020) to chromosome 11, KRAS2 (OMIM Ref. No. 190070) to chromosome 12, and NRAS1 to chromosome 1. Addendum in proof indicated that the same laboratory had assigned NRAS1 to 1p21–cen. The NRAS oncogene is distinct from the SK oncogene (OMIM Ref. No. 164780) in several characteristics (Balazs, 1983) and has a different location on chromosome 1. By somatic cell hybrid studies and by in situ hybridization, Rabin et al. (1984) assigned the NRAS gene to 1p11–p13. By in situ hybridization, Popescu et al. (1985) also assigned the NRAS locus to 1p11–p13. Povey et al. (1985) reviewed the conflicting evidence on the site of NRAS on 1p. They found evidence favoring both 1p22 and 1p12–p11. Dracopoli and Meisler (1990) concluded from linkage analysis and pulsed field gel electrophoresis that TSHB (OMIM Ref. No. 188540), NGFB (OMIM Ref. No. 162030), and NRAS form a tightly

linked gene cluster located in the same chromosomal band. Their location proximal to the AMY2B gene in 1p21 and close linkage to the alpha-satellite centromeric repeat D1Z5 provided strong evidence that the correct assignment for these 3 loci is 1p13 and not 1p22. Mitchell et al. (1995) localized NRAS to 1p13.2 and CD2 (OMIM Ref. No. 186990) and NGFB to 1p13.1. They concluded that the order is as follows: cen--CD2--NGFB--NRAS--tel. Using the allele-specific amplification method (ARMS), a highly sensitive 1-stage allele-specific PCR, Bezieau et al. (2001) evaluated the incidence of NRAS- and KRAS2-activating mutations (in codons 12, 13, and 61) in 62 patients with monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), or primary plasma cell leukemia (PPCL), and in human myeloma cell lines (HMCL). Mutations in one or the other gene, or in both, were found in 54.5% of MM patients at diagnosis (but in 81% at the time of relapse), 50% of PPCL patients, and 50% of 16 HMCL patients. In contrast, the occurrence of such mutations was very low in MGUS and indolent MM (12.5%). KRAS2 mutations were always more frequent than NRAS mutations. Bezieau et al. (2001) concluded that these early mutations may play a major role in the oncogenesis

of multiple myeloid myeloma and primary plasma cell leukemia.

[18042] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18043] Bezieau, S.; Devilder, M.-C.; Avet-Loiseau, H.; Mellerin, M.-P.; Puthier, D.; Pennarun, E.; Rapp, M.-J.; Harousseau, J.-L.; Moisan, J.-P.; Bataille, R. : High incidence of N and K-Ras activating mutations in multiple myeloma and primary plasma cell leukemia at diagnosis. Hum. Mutat. 18: 212-224, 2001. ; and

[18044] Mitchell, E. L. D.; Jones, D.; White, G. R. M.; Varley, J. M.; Santibanez Koref, M. F. : Determination of the gene order of the three loci CD2, NGFB, and NRAS at human chromosome band.

[18045] Further studies establishing the function and utilities of NRAS are found in John Hopkins OMIM database record ID 164790, and in cited publications numbered 2257-2263, 12417-2266, 2238-2239, 2267-227 and 12743-12744 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC154739 (Accession XM\_098602) is another VGAM351 host target gene. LOC154739 BINDING SITE is HOST TARGET binding

site found in the 5' untranslated region of mRNA encoded by LOC154739, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154739 BINDING SITE, designated SEQ ID:41714, to the nucleotide sequence of VGAM351 RNA, herein designated VGAM RNA, also designated SEQ ID:3062.

[18046] Another function of VGAM351 is therefore inhibition of LOC154739 (Accession XM\_098602). Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154739. LOC203276 (Accession XM\_117523) is another VGAM351 host target gene. LOC203276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203276 BINDING SITE, designated SEQ ID:43481, to the nucleotide sequence of VGAM351 RNA, herein designated VGAM RNA, also designated SEQ ID:3062.

[18047] Another function of VGAM351 is therefore inhibition of

LOC203276 (Accession XM\_117523). Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203276. LOC203305 (Accession XM\_117529) is another VGAM351 host target gene. LOC203305 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203305, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203305 BINDING SITE, designated SEQ ID:43505, to the nucleotide sequence of VGAM351 RNA, herein designated VGAM RNA, also designated SEQ ID:3062.

[18048] Another function of VGAM351 is therefore inhibition of LOC203305 (Accession XM\_117529). Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203305. LOC254243 (Accession XM\_173233) is another VGAM351 host target gene. LOC254243 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254243, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC254243 BINDING SITE, designated SEQ ID:46507, to the nucleotide sequence of VGAM351 RNA, herein designated VGAM RNA, also designated SEQ ID:3062.

[18049] Another function of VGAM351 is therefore inhibition of LOC254243 (Accession XM\_173233). Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254243. LOC255870 (Accession XM\_170628) is another VGAM351 host target gene. LOC255870 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255870, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255870 BINDING SITE, designated SEQ ID:45405, to the nucleotide sequence of VGAM351 RNA, herein designated VGAM RNA, also designated SEQ ID:3062.

[18050] Another function of VGAM351 is therefore inhibition of LOC255870 (Accession XM\_170628). Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255870. LOC90038 (Accession XM\_028305) is an-

other VGAM351 host target gene. LOC90038 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90038 BINDING SITE, designated SEQ ID:30644, to the nucleotide sequence of VGAM351 RNA, herein designated VGAM RNA, also designated SEQ ID:3062.

[18051] Another function of VGAM351 is therefore inhibition of LOC90038 (Accession XM\_028305). Accordingly, utilities of VGAM351 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90038. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 352 (VGAM352) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18052] VGAM352 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM352 was detected is described



hereinabove with reference to Figs. 1–8.

[18053] VGAM352 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM352 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18054] VGAM352 gene encodes a VGAM352 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM352 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM352 precursor RNA is designated SEQ ID:338, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:338 is located at position 4158 relative to the genome of Avian Infectious Bronchitis Virus.

[18055] VGAM352 precursor RNA folds onto itself, forming VGAM352 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18056] An enzyme complex designated DICER COMPLEX, `dices` the VGAM352 folded precursor RNA into VGAM352 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM352 RNA is designated SEQ ID:3063, and is provided hereinbelow with reference to the sequence listing part.

[18057] VGAM352 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM352 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM352 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18058] VGAM352 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM352 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM352 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM352 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM352 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18059] The complementary binding of VGAM352 RNA, herein designated VGAM RNA, to host target binding sites on VGAM352 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM352 host target RNA into VGAM352 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18060] It is appreciated that VGAM352 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM352 host target genes. The mRNA of each one of this plurality of VGAM352 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM352 RNA, herein designated VGAM RNA, and which when bound by VGAM352 RNA causes inhibition of translation of respective one or more VGAM352 host target proteins.

[18061] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM352 gene, herein designated VGAM GENE, on one or more VGAM352 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18062] It is yet further appreciated that a function of VGAM352 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM352 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM352 correlate with, and may be deduced from, the identity of the host target genes which VGAM352 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18063] Nucleotide sequences of the VGAM352 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM352 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM352 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM352 are further described hereinbelow with reference to Table 1.

[18064] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM352 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM352 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18065] As mentioned hereinabove with reference to Fig. 1, a function of VGAM352 gene, herein designated VGAM is inhibition of expression of VGAM352 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM352 correlate with, and may be deduced from, the identity of the target genes which VGAM352 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18066] AXL Receptor Tyrosine Kinase (AXL, Accession NM\_001699) is a VGAM352 host target gene. AXL BINDING SITE1 and AXL BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by AXL, corresponding to HOST TARGET binding sites

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AXL BINDING SITE1 and AXL BINDING SITE2, designated SEQ ID:7425 and SEQ ID:22446 respectively, to the nucleotide sequence of VGAM352 RNA, herein designated VGAM RNA, also designated SEQ ID:3063.

[18067] A function of VGAM352 is therefore inhibition of AXL Receptor Tyrosine Kinase (AXL, Accession NM\_001699). Accordingly, utilities of VGAM352 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AXL. FLJ20972 (Accession NM\_025030) is another VGAM352 host target gene. FLJ20972 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20972, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20972 BINDING SITE, designated SEQ ID:24627, to the nucleotide sequence of VGAM352 RNA, herein designated VGAM RNA, also designated SEQ ID:3063.

[18068] Another function of VGAM352 is therefore inhibition of FLJ20972 (Accession NM\_025030). Accordingly, utilities of VGAM352 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ20972. LOC200399 (Accession XM\_114226) is another VGAM352 host target gene. LOC200399 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200399, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200399 BINDING SITE, designated SEQ ID:42812, to the nucleotide sequence of VGAM352 RNA, herein designated VGAM RNA, also designated SEQ ID:3063.

[18069] Another function of VGAM352 is therefore inhibition of LOC200399 (Accession XM\_114226). Accordingly, utilities of VGAM352 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200399. LOC90786 (Accession XM\_034127) is another VGAM352 host target gene. LOC90786 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90786, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90786 BINDING SITE, designated SEQ ID:32013, to the



nucleotide sequence of VGAM352 RNA, herein designated VGAM RNA, also designated SEQ ID:3063.

[18070] Another function of VGAM352 is therefore inhibition of LOC90786 (Accession XM\_034127). Accordingly, utilities of VGAM352 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90786. LOC92267 (Accession XM\_043979) is another VGAM352 host target gene. LOC92267 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92267, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92267 BINDING SITE, designated SEQ ID:34057, to the nucleotide sequence of VGAM352 RNA, herein designated VGAM RNA, also designated SEQ ID:3063.

[18071] Another function of VGAM352 is therefore inhibition of LOC92267 (Accession XM\_043979). Accordingly, utilities of VGAM352 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92267. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 353 (VGAM353) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18072] VGAM353 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM353 was detected is described hereinabove with reference to Figs. 1–8.

[18073] VGAM353 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM353 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18074] VGAM353 gene encodes a VGAM353 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM353 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM353 precursor RNA is designated SEQ ID:339, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:339 is located at position 6850 relative to the genome of Avian Infectious Bronchitis Virus.

[18075] VGAM353 precursor RNA folds onto itself, forming VGAM353 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18076] An enzyme complex designated DICER COMPLEX, `dices` the VGAM353 folded precursor RNA into VGAM353 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM353 RNA is designated SEQ ID:3064, and is provided hereinbelow with reference to the sequence listing part.

[18077] VGAM353 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM353 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM353 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18078] VGAM353 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM353 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM353 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM353 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM353 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18079] The complementary binding of VGAM353 RNA, herein designated VGAM RNA, to host target binding sites on VGAM353 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM353 host target RNA into VGAM353 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18080] It is appreciated that VGAM353 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM353 host target genes. The mRNA of each one of this plurality of VGAM353 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM353 RNA, herein designated VGAM RNA, and which when bound by VGAM353 RNA causes inhibition of translation of respective one or more VGAM353 host target proteins.

[18081] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM353 gene, herein designated VGAM GENE, on one or more VGAM353 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18082] It is yet further appreciated that a function of VGAM353 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM353 correlate with, and may be deduced from, the

identity of the host target genes which VGAM353 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18083] Nucleotide sequences of the VGAM353 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM353 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM353 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM353 are further described hereinbelow with reference to Table 1.

[18084] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM353 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM353 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18085] As mentioned hereinabove with reference to Fig. 1, a function of VGAM353 gene, herein designated VGAM is inhibition of expression of VGAM353 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM353 correlate with, and may be deduced from, the identity of the target genes which VGAM353

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18086] Golgi Associated, Gamma Adaptin Ear Containing, ARF Binding Protein 3 (GGA3, Accession NM\_014001) is a VGAM353 host target gene. GGA3 BINDING SITE1 and GGA3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GGA3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GGA3 BINDING SITE1 and GGA3 BINDING SITE2, designated SEQ ID:15197 and SEQ ID:28900 respectively, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18087] A function of VGAM353 is therefore inhibition of Golgi Associated, Gamma Adaptin Ear Containing, ARF Binding Protein 3 (GGA3, Accession NM\_014001), a gene which may play a role in the regulation of membrane traffic through the trans-golgi network. Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GGA3. The function of GGA3 has been established by previous



studies. For general information on cloning and function of the GGA family, see the entry for GGA1 (OMIM Ref. No. 606004).

[18088] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18089] Doray, B.; Ghosh, P.; Griffith, J.; Geuze, H. J.; Kornfeld, S. : Cooperation of GGAs and AP-1 in packaging MPRs at the trans-Golgi network. Science 297: 1700-1703, 2002. ; and

[18090] Hirst, J.; Lui, W. W. Y.; Bright, N. A.; Totty, N.; Seaman, M. N. J.; Robinson, M. S. : A family of proteins with gamma-adaptin and VHS domains that facilitate trafficking between the.

[18091] Further studies establishing the function and utilities of GGA3 are found in John Hopkins OMIM database record ID 606006, and in cited publications numbered 4436, 1259 and 10969 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 20 Open Reading Frame 106 (C20orf106, Accession NM\_080824) is another VGAM353 host target gene. C20orf106 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of

mRNA encoded by C20orf106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf106 BINDING SITE, designated SEQ ID:28091, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18092] Another function of VGAM353 is therefore inhibition of Chromosome 20 Open Reading Frame 106 (C20orf106, Accession NM\_080824). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf106. Epiregulin (EREG, Accession NM\_001432) is another VGAM353 host target gene. EREG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EREG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EREG BINDING SITE, designated SEQ ID:7155, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18093] Another function of VGAM353 is therefore inhibition of

Epiregulin (EREG, Accession NM\_001432). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EREG. KIAA1046 (Accession NM\_014928) is another VGAM353 host target gene. KIAA1046 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1046, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1046 BINDING SITE, designated SEQ ID:17217, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18094] Another function of VGAM353 is therefore inhibition of KIAA1046 (Accession NM\_014928). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1046. Mitochondrial Ribosomal Protein L20 (MRPL20, Accession NM\_017971) is another VGAM353 host target gene. MRPL20 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MRPL20, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of MRPL20 BINDING SITE, designated SEQ ID:19698, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18095] Another function of VGAM353 is therefore inhibition of Mitochondrial Ribosomal Protein L20 (MRPL20, Accession NM\_017971). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MRPL20. NTT73 (Accession NM\_018057) is another VGAM353 host target gene. NTT73 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NTT73, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NTT73 BINDING SITE, designated SEQ ID:19824, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18096] Another function of VGAM353 is therefore inhibition of NTT73 (Accession NM\_018057). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with NTT73. Protein O-fucosyltransferase 1 (POFUT1, Accession XM\_047011) is another VGAM353 host target gene. POFUT1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by POFUT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POFUT1 BINDING SITE, designated SEQ ID:34884, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18097] Another function of VGAM353 is therefore inhibition of Protein O-fucosyltransferase 1 (POFUT1, Accession XM\_047011). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POFUT1. LOC146237 (Accession XM\_096954) is another VGAM353 host target gene. LOC146237 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC146237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of LOC146237 BINDING SITE, designated SEQ ID:40664, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18098] Another function of VGAM353 is therefore inhibition of LOC146237 (Accession XM\_096954). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146237. LOC148562 (Accession XM\_086240) is another VGAM353 host target gene. LOC148562 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148562, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148562 BINDING SITE, designated SEQ ID:38566, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18099] Another function of VGAM353 is therefore inhibition of LOC148562 (Accession XM\_086240). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148562. LOC200197 (Accession XM\_114148) is an-

other VGAM353 host target gene. LOC200197 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200197, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200197 BINDING SITE, designated SEQ ID:42732, to the nucleotide sequence of VGAM353 RNA, herein designated VGAM RNA, also designated SEQ ID:3064.

[18100] Another function of VGAM353 is therefore inhibition of LOC200197 (Accession XM\_114148). Accordingly, utilities of VGAM353 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200197. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 354 (VGAM354) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18101] VGAM354 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM354 was detected is described

hereinabove with reference to Figs. 1–8.

[18102] VGAM354 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM354 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18103] VGAM354 gene encodes a VGAM354 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM354 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM354 precursor RNA is designated SEQ ID:340, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:340 is located at position 7380 relative to the genome of Avian Infectious Bronchitis Virus.

[18104] VGAM354 precursor RNA folds onto itself, forming VGAM354 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an



accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18105] An enzyme complex designated DICER COMPLEX, `dices` the VGAM354 folded precursor RNA into VGAM354 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 53%) nucleotide sequence of VGAM354 RNA is designated SEQ ID:3065, and is provided hereinbelow with reference to the sequence listing part.

[18106] VGAM354 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM354 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM354 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18107] VGAM354 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM354 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM354 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM354 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM354 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18108] The complementary binding of VGAM354 RNA, herein designated VGAM RNA, to host target binding sites on VGAM354 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM354 host target RNA into VGAM354 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18109] It is appreciated that VGAM354 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM354 host target genes. The mRNA of each one of this plurality of VGAM354 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM354 RNA, herein designated VGAM RNA, and which when bound by VGAM354 RNA causes inhibition of translation of respective one or more VGAM354 host target proteins.

[18110] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM354 gene, herein designated VGAM GENE, on one or more VGAM354 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18111] It is yet further appreciated that a function of VGAM354 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM354 correlate with, and may be deduced from, the identity of the host target genes which VGAM354 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18112] Nucleotide sequences of the VGAM354 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM354 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM354 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM354 are further described hereinbelow with reference to Table 1.

[18113] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM354 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM354 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18114] As mentioned hereinabove with reference to Fig. 1, a function of VGAM354 gene, herein designated VGAM is inhibition of expression of VGAM354 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM354 correlate with, and may be deduced from, the identity of the target genes which VGAM354 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18115] Myotubularin Related Protein 2 (MTMR2, Accession NM\_016156) is a VGAM354 host target gene. MTMR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MTMR2, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTMR2 BINDING SITE, designated SEQ ID:18242, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18116] A function of VGAM354 is therefore inhibition of Myotubularin Related Protein 2 (MTMR2, Accession NM\_016156). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTMR2. Baculoviral IAP Repeat-containing 1 (BIRC1, Accession NM\_004536) is another VGAM354 host target gene. BIRC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BIRC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BIRC1 BINDING SITE, designated SEQ ID:10880, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18117] Another function of VGAM354 is therefore inhibition of Baculoviral IAP Repeat-containing 1 (BIRC1, Accession NM\_004536). Accordingly, utilities of VGAM354 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with BIRC1. Death-associated Protein Kinase 2 (DAPK2, Accession NM\_014326) is another VGAM354 host target gene. DAPK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DAPK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAPK2 BINDING SITE, designated SEQ ID:15633, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18118] Another function of VGAM354 is therefore inhibition of Death-associated Protein Kinase 2 (DAPK2, Accession NM\_014326). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAPK2. FLJ20128 (Accession NM\_017679) is another VGAM354 host target gene. FLJ20128 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20128, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of FLJ20128 BINDING SITE, designated SEQ ID:19221, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18119] Another function of VGAM354 is therefore inhibition of FLJ20128 (Accession NM\_017679). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20128. Olfactory Receptor, Family 2, Subfamily C, Member 3 (OR2C3, Accession XM\_060575) is another VGAM354 host target gene. OR2C3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OR2C3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OR2C3 BINDING SITE, designated SEQ ID:37174, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18120] Another function of VGAM354 is therefore inhibition of Olfactory Receptor, Family 2, Subfamily C, Member 3 (OR2C3, Accession XM\_060575). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with OR2C3. RAP2B, Member of RAS Oncogene Family (RAP2B, Accession XM\_171061) is another VGAM354 host target gene. RAP2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAP2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAP2B BINDING SITE, designated SEQ ID:45859, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18121] Another function of VGAM354 is therefore inhibition of RAP2B, Member of RAS Oncogene Family (RAP2B, Accession XM\_171061). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAP2B. RODH-4 (Accession NM\_003708) is another VGAM354 host target gene. RODH-4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RODH-4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of RODH-4 BINDING SITE, designated SEQ ID:9806, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18122] Another function of VGAM354 is therefore inhibition of RODH-4 (Accession NM\_003708). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RODH-4. LOC151742 (Accession NM\_139245) is another VGAM354 host target gene. LOC151742 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151742, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151742 BINDING SITE, designated SEQ ID:29241, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18123] Another function of VGAM354 is therefore inhibition of LOC151742 (Accession NM\_139245). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151742. LOC219529 (Accession XM\_167563) is an-

other VGAM354 host target gene. LOC219529 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219529, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219529 BINDING SITE, designated SEQ ID:44675, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18124] Another function of VGAM354 is therefore inhibition of LOC219529 (Accession XM\_167563). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219529. LOC90459 (Accession XM\_031826) is another VGAM354 host target gene. LOC90459 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90459, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90459 BINDING SITE, designated SEQ ID:31491, to the nucleotide sequence of VGAM354 RNA, herein designated VGAM RNA, also designated SEQ ID:3065.

[18125] Another function of VGAM354 is therefore inhibition of LOC90459 (Accession XM\_031826). Accordingly, utilities of VGAM354 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90459. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 355 (VGAM355) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18126] VGAM355 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM355 was detected is described hereinabove with reference to Figs. 1–8.

[18127] VGAM355 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM355 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18128] VGAM355 gene encodes a VGAM355 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM355

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM355 precursor RNA is designated SEQ ID:341, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:341 is located at position 931 relative to the genome of Avian Infectious Bronchitis Virus.

[18129] VGAM355 precursor RNA folds onto itself, forming VGAM355 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18130] An enzyme complex designated DICER COMPLEX, `dices` the VGAM355 folded precursor RNA into VGAM355 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 47%) nucleotide sequence of VGAM355 RNA is designated SEQ ID:3066, and is provided hereinbelow with reference to the sequence listing part.

[18131] VGAM355 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM355 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM355 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18132] VGAM355 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM355 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM355 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM355 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM355 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18133] The complementary binding of VGAM355 RNA, herein designated VGAM RNA, to host target binding sites on VGAM355 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM355 host target RNA into VGAM355 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18134] It is appreciated that VGAM355 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM355 host target genes. The mRNA of each one of this plurality of VGAM355 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM355 RNA, herein designated VGAM RNA, and which when bound by VGAM355 RNA causes inhibition of translation of respective one or more VGAM355 host target proteins.

[18135] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM355 gene, herein designated VGAM GENE, on one or more VGAM355 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).



[18136] It is yet further appreciated that a function of VGAM355 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM355 correlate with, and may be deduced from, the identity of the host target genes which VGAM355 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18137] Nucleotide sequences of the VGAM355 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM355 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM355 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM355 are further described hereinbelow with reference to Table 1.

[18138] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM355 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM355 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[18139] As mentioned hereinabove with reference to Fig. 1, a function of VGAM355 gene, herein designated VGAM is inhibition of expression of VGAM355 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM355 correlate with, and may be deduced from, the identity of the target genes which VGAM355 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18140] B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993) is a VGAM355 host target gene. BCL7A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL7A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL7A BINDING SITE, designated SEQ ID:21987, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18141] A function of VGAM355 is therefore inhibition of B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with BCL7A. Macrophage Scavenger Receptor 1 (MSR1, Accession NM\_138715) is another VGAM355 host target gene. MSR1 BINDING SITE1 and MSR1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MSR1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSR1 BINDING SITE1 and MSR1 BINDING SITE2, designated SEQ ID:28961 and SEQ ID:28963 respectively, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18142] Another function of VGAM355 is therefore inhibition of Macrophage Scavenger Receptor 1 (MSR1, Accession NM\_138715), a gene which plays a role in endocytosis of macromolecules. Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSR1. The function of MSR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM176. Vacuolar Protein Sorting 41 (yeast) (VPS41, Accession NM\_014396) is another VGAM355 host target

gene. VPS41 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by VPS41, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VPS41 BINDING SITE, designated SEQ ID:15736, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18143] Another function of VGAM355 is therefore inhibition of Vacuolar Protein Sorting 41 (yeast) (VPS41, Accession NM\_014396). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VPS41. KIAA1538 (Accession XM\_049474) is another VGAM355 host target gene. KIAA1538 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1538 BINDING SITE, designated SEQ ID:35435, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ

ID:3066.

[18144] Another function of VGAM355 is therefore inhibition of KIAA1538 (Accession XM\_049474). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1538. KIAA1712 (Accession XM\_041497) is another VGAM355 host target gene. KIAA1712 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1712, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1712 BINDING SITE, designated SEQ ID:33538, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18145] Another function of VGAM355 is therefore inhibition of KIAA1712 (Accession XM\_041497). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1712. KIAA1906 (Accession XM\_055095) is another VGAM355 host target gene. KIAA1906 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1906, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1906 BINDING SITE, designated SEQ ID:36232, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18146] Another function of VGAM355 is therefore inhibition of KIAA1906 (Accession XM\_055095). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1906. Paternally Expressed 10 (PEG10, Accession NM\_015068) is another VGAM355 host target gene. PEG10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PEG10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PEG10 BINDING SITE, designated SEQ ID:17426, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18147] Another function of VGAM355 is therefore inhibition of Paternally Expressed 10 (PEG10, Accession NM\_015068).

Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PEG10. Solute Carrier Family 2 (facilitated glucose transporter), Member 10 (SLC2A10, Accession NM\_030777) is another VGAM355 host target gene. SLC2A10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC2A10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC2A10 BINDING SITE, designated SEQ ID:25064, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18148] Another function of VGAM355 is therefore inhibition of Solute Carrier Family 2 (facilitated glucose transporter), Member 10 (SLC2A10, Accession NM\_030777). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC2A10. LOC143153 (Accession XM\_084440) is another VGAM355 host target gene. LOC143153 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143153, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143153 BINDING SITE, designated SEQ ID:37582, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18149] Another function of VGAM355 is therefore inhibition of LOC143153 (Accession XM\_084440). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143153. LOC143154 (Accession XM\_084441) is another VGAM355 host target gene. LOC143154 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143154, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143154 BINDING SITE, designated SEQ ID:37588, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18150] Another function of VGAM355 is therefore inhibition of LOC143154 (Accession XM\_084441). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with LOC143154. LOC144289 (Accession XM\_096565) is another VGAM355 host target gene. LOC144289 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC144289, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144289 BINDING SITE, designated SEQ ID:40398, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18151] Another function of VGAM355 is therefore inhibition of LOC144289 (Accession XM\_096565). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144289. LOC219294 (Accession XM\_167566) is another VGAM355 host target gene. LOC219294 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC219294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219294 BINDING SITE, designated SEQ ID:44689, to

the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18152] Another function of VGAM355 is therefore inhibition of LOC219294 (Accession XM\_167566). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219294. LOC219295 (Accession XM\_167565) is another VGAM355 host target gene. LOC219295 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219295, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219295 BINDING SITE, designated SEQ ID:44683, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18153] Another function of VGAM355 is therefore inhibition of LOC219295 (Accession XM\_167565). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219295. LOC91170 (Accession XM\_036612) is another VGAM355 host target gene. LOC91170 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC91170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91170 BINDING SITE, designated SEQ ID:32479, to the nucleotide sequence of VGAM355 RNA, herein designated VGAM RNA, also designated SEQ ID:3066.

[18154] Another function of VGAM355 is therefore inhibition of LOC91170 (Accession XM\_036612). Accordingly, utilities of VGAM355 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91170. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 356 (VGAM356) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18155] VGAM356 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM356 was detected is described hereinabove with reference to Figs. 1–8.

[18156] VGAM356 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM356 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18157] VGAM356 gene encodes a VGAM356 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM356 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM356 precursor RNA is designated SEQ ID:342, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:342 is located at position 6336 relative to the genome of Avian Infectious Bronchitis Virus.

[18158] VGAM356 precursor RNA folds onto itself, forming VGAM356 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18159] An enzyme complex designated DICER COMPLEX, `dices` the VGAM356 folded precursor RNA into VGAM356 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM356 RNA is designated SEQ ID:3067, and is provided hereinbelow with reference to the sequence listing part.

[18160] VGAM356 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM356 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM356 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18161] VGAM356 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM356 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM356 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM356 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM356 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18162] The complementary binding of VGAM356 RNA, herein designated VGAM RNA, to host target binding sites on VGAM356 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM356 host tar-

get RNA into VGAM356 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18163] It is appreciated that VGAM356 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM356 host target genes. The mRNA of each one of this plurality of VGAM356 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM356 RNA, herein designated VGAM RNA, and which when bound by VGAM356 RNA causes inhibition of translation of respective one or more VGAM356 host target proteins.

[18164] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM356 gene, herein designated VGAM GENE, on one or more VGAM356 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18165] It is yet further appreciated that a function of VGAM356 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM356 correlate with, and may be deduced from, the identity of the host target genes which VGAM356 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18166] Nucleotide sequences of the VGAM356 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM356 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM356 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM356 are further



described hereinbelow with reference to Table 1.

[18167] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM356 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM356 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18168] As mentioned hereinabove with reference to Fig. 1, a function of VGAM356 gene, herein designated VGAM is inhibition of expression of VGAM356 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM356 correlate with, and may be deduced from, the identity of the target genes which VGAM356 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18169] CDC-like Kinase 2 (CLK2, Accession NM\_001291) is a VGAM356 host target gene. CLK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLK2 BINDING SITE,

designated SEQ ID:6971, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18170] A function of VGAM356 is therefore inhibition of CDC-like Kinase 2 (CLK2, Accession NM\_001291), a gene which catalyzes the phosphorylation of proteins. Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLK2. The function of CLK2 has been established by previous studies. The protein kinases are a family of enzymes that catalyze the phosphorylation of proteins and are classified according to the amino acid that acts as the phosphate acceptor. Hanes et al. (1994) cloned human ovarian follicle cDNAs encoding the novel serine/threonine kinase CLK2 based on their high sequence identity to human and mouse protein kinase CLK1 (CLK; 601951) cDNAs. The authors identified 2 alternative CLK2 cDNAs of different lengths that represent differentially spliced CLK2 transcripts; these mRNAs coexist at varying ratios in human prostate, testis, leukocytes, and muscle. The longer CLK2 cDNA encodes a predicted 499-amino acid protein that has a nonconserved N-terminal domain, a highly conserved C-terminal kinase domain, and multiple

potential phosphorylation sites. This CLK2 isoform has 61% and 56% sequence identity with the CLK3 (OMIM Ref. No. 602990) and CLK1 proteins, respectively. The shorter cDNA contains an internal deletion corresponding to an 88-bp exon, resulting in a predicted 139-amino acid protein that lacks the kinase domain. Southern blot analysis of human genomic DNA suggested that CLK2 is a single-copy gene. Nothwang et al. (2001) reported a translocation t(1;19)(q21.3;q13.2) in a female with mental retardation, ataxia, and atrophy of the brain. Sequence analysis of the breakpoints revealed an Alu repeat-mediated mechanism of recombination that led to truncation of CLK2 and PAFAH1B3 (OMIM Ref. No. 603074), the gene product of which interacts with LIS1 (OMIM Ref. No. 601545) as part of the heterotrimeric G protein complex PAFAH1B. One expressed fusion gene encoded the first 136 amino acids of PAFAH1B3, followed by the complete CLK2 protein. Truncated PAFAH1B3 protein lost its potential to interact with LIS1, whereas CLK2 activity was conserved within the fusion protein. These data emphasized the importance of PAFAH1B in brain development and function.

[18171] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [18172] Hanes, J.; von der Kammer, H.; Klaudiny, J.; Scheit, K. H. : Characterization by cDNA cloning of two new human protein kinases: evidence by sequence comparison of a new family of mammalian protein kinases. J. Molec. Biol. 244: 665–672, 1994. ; and
- [18173] Nothwang, H. G.; Kim, H. G.; Aoki, J.; Geisterfer, M.; Kubart, S.; Wegner, R. D.; van Moers, A.; Ashworth, L. K.; Haaf, T.; Bell, J.; Arai, H.; Tommerup, N.; Ropers, H. H.; Wirth, J. .:
- [18174] Further studies establishing the function and utilities of CLK2 are found in John Hopkins OMIM database record ID 602989, and in cited publications numbered 669 and 6700 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Eukaryotic Translation Initiation Factor 2C, 1 (EIF2C1, Accession NM\_012199) is another VGAM356 host target gene. EIF2C1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF2C1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of EIF2C1 BINDING SITE, designated SEQ ID:14498, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18175] Another function of VGAM356 is therefore inhibition of Eukaryotic Translation Initiation Factor 2C, 1 (EIF2C1, Accession NM\_012199), a gene which plays an important role in the eukaryotic peptide chain initiation process. Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF2C1. The function of EIF2C1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM118. Fms-related Tyrosine Kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor) (FLT1, Accession NM\_002019) is another VGAM356 host target gene. FLT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLT1 BINDING SITE, designated SEQ ID:7762, to the nucleotide sequence

of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18176] Another function of VGAM356 is therefore inhibition of Fms-related Tyrosine Kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor) (FLT1, Accession NM\_002019). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLT1. Homeo Box D4 (HOXD4, Accession NM\_014621) is another VGAM356 host target gene. HOXD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HOXD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HOXD4 BINDING SITE, designated SEQ ID:15976, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18177] Another function of VGAM356 is therefore inhibition of Homeo Box D4 (HOXD4, Accession NM\_014621), a gene which is part of a developmental regulatory system. Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with HOXD4. The function of HOXD4 and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM330. Myelin Oligodendrocyte Glycoprotein (MOG, Accession NM\_002433) is another VGAM356 host target gene. MOG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MOG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MOG BINDING SITE, designated SEQ ID:8277, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18178] Another function of VGAM356 is therefore inhibition of Myelin Oligodendrocyte Glycoprotein (MOG, Accession NM\_002433). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MOG. Sal-like 2 (Drosophila) (SALL2, Accession XM\_033473) is another VGAM356 host target gene. SALL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SALL2, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SALL2 BINDING SITE, designated SEQ ID:31934, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18179] Another function of VGAM356 is therefore inhibition of Sal-like 2 (Drosophila) (SALL2, Accession XM\_033473). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SALL2. Chromosome 20 Open Reading Frame 130 (C20orf130, Accession XM\_029741) is another VGAM356 host target gene. C20orf130 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf130, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf130 BINDING SITE, designated SEQ ID:30933, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18180] Another function of VGAM356 is therefore inhibition of Chromosome 20 Open Reading Frame 130 (C20orf130,



Accession XM\_029741). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf130. Chromosome 8 Open Reading Frame 17 (C8orf17, Accession NM\_020237) is another VGAM356 host target gene.

C8orf17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C8orf17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C8orf17 BINDING SITE, designated SEQ ID:21505, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18181] Another function of VGAM356 is therefore inhibition of Chromosome 8 Open Reading Frame 17 (C8orf17, Accession NM\_020237). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C8orf17. Calcium/calmodulin-dependent Protein Kinase Kinase 2, Beta (CAMKK2, Accession NM\_006549) is another VGAM356 host target gene. CAMKK2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA

encoded by CAMKK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAMKK2 BINDING SITE, designated SEQ ID:13308, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18182] Another function of VGAM356 is therefore inhibition of Calcium/calmodulin-dependent Protein Kinase Kinase 2, Beta (CAMKK2, Accession NM\_006549). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAMKK2. DIM1 (Accession NM\_006701) is another VGAM356 host target gene. DIM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DIM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DIM1 BINDING SITE, designated SEQ ID:13524, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18183] Another function of VGAM356 is therefore inhibition of

DIM1 (Accession NM\_006701). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIM1. Elongation of Very Long Chain Fatty Acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 2 (ELOVL2, Accession NM\_017770) is another VGAM356 host target gene. ELOVL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ELOVL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELOVL2 BINDING SITE, designated SEQ ID:19386, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18184] Another function of VGAM356 is therefore inhibition of Elongation of Very Long Chain Fatty Acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 2 (ELOVL2, Accession NM\_017770). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELOVL2. FLJ14440 (Accession NM\_032784) is another VGAM356 host target gene. FLJ14440 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

FLJ14440, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14440 BINDING SITE, designated SEQ ID:26530, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18185] Another function of VGAM356 is therefore inhibition of FLJ14440 (Accession NM\_032784). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14440. FLJ21687 (Accession NM\_024859) is another VGAM356 host target gene. FLJ21687 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21687 BINDING SITE, designated SEQ ID:24288, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18186] Another function of VGAM356 is therefore inhibition of FLJ21687 (Accession NM\_024859). Accordingly, utilities of

VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21687. KIAA0798 (Accession NM\_014650) is another VGAM356 host target gene. KIAA0798 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0798, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0798 BINDING SITE, designated SEQ ID:16065, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18187] Another function of VGAM356 is therefore inhibition of KIAA0798 (Accession NM\_014650). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0798. KIAA1404 (Accession XM\_030494) is another VGAM356 host target gene. KIAA1404 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1404, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1404 BINDING SITE, designated SEQ ID:31047, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18188] Another function of VGAM356 is therefore inhibition of KIAA1404 (Accession XM\_030494). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1404. KIAA1456 (Accession XM\_040100) is another VGAM356 host target gene. KIAA1456 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1456, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1456 BINDING SITE, designated SEQ ID:33261, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18189] Another function of VGAM356 is therefore inhibition of KIAA1456 (Accession XM\_040100). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1456. KIAA1580 (Accession XM\_045271) is another VGAM356 host target gene. KIAA1580 BINDING SITE is

HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1580, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1580 BINDING SITE, designated SEQ ID:34404, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18190] Another function of VGAM356 is therefore inhibition of KIAA1580 (Accession XM\_045271). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1580. KIAA1950 (Accession XM\_166532) is another VGAM356 host target gene. KIAA1950 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1950, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1950 BINDING SITE, designated SEQ ID:44482, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18191] Another function of VGAM356 is therefore inhibition of

KIAA1950 (Accession XM\_166532). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1950. MYLE (Accession NM\_014015) is another VGAM356 host target gene. MYLE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYLE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYLE BINDING SITE, designated SEQ ID:15233, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18192] Another function of VGAM356 is therefore inhibition of MYLE (Accession NM\_014015). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYLE. Peptidyl Arginine Deiminase, Type I (PADI1, Accession XM\_030498) is another VGAM356 host target gene. PADI1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PADI1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-



illustrates the complementarity of the nucleotide sequences of PADI1 BINDING SITE, designated SEQ ID:31053, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18193] Another function of VGAM356 is therefore inhibition of Peptidyl Arginine Deiminase, Type I (PADI1, Accession XM\_030498). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PADI1. Solute Carrier Family 17 (sodium-dependent inorganic phosphate cotransporter), Member 6 (SLC17A6, Accession NM\_020346) is another VGAM356 host target gene. SLC17A6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC17A6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC17A6 BINDING SITE, designated SEQ ID:21594, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18194] Another function of VGAM356 is therefore inhibition of Solute Carrier Family 17 (sodium-dependent inorganic phosphate cotransporter), Member 6 (SLC17A6, Accession

NM\_020346). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC17A6. LOC116411 (Accession XM\_058095) is another VGAM356 host target gene. LOC116411 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC116411, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC116411 BINDING SITE, designated SEQ ID:36564, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18195] Another function of VGAM356 is therefore inhibition of LOC116411 (Accession XM\_058095). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116411. LOC143308 (Accession XM\_096411) is another VGAM356 host target gene. LOC143308 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC143308, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC143308 BINDING SITE, designated SEQ ID:40346, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18196] Another function of VGAM356 is therefore inhibition of LOC143308 (Accession XM\_096411). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143308. LOC145384 (Accession XM\_085128) is another VGAM356 host target gene. LOC145384 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145384, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145384 BINDING SITE, designated SEQ ID:37860, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18197] Another function of VGAM356 is therefore inhibition of LOC145384 (Accession XM\_085128). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145384. LOC85479 (Accession NM\_033105) is an-

other VGAM356 host target gene. LOC85479 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC85479, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC85479 BINDING SITE, designated SEQ ID:26956, to the nucleotide sequence of VGAM356 RNA, herein designated VGAM RNA, also designated SEQ ID:3067.

[18198] Another function of VGAM356 is therefore inhibition of LOC85479 (Accession NM\_033105). Accordingly, utilities of VGAM356 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC85479. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 357 (VGAM357) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18199] VGAM357 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM357 was detected is described

hereinabove with reference to Figs. 1–8.

[18200] VGAM357 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM357 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18201] VGAM357 gene encodes a VGAM357 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM357 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM357 precursor RNA is designated SEQ ID:343, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:343 is located at position 1864 relative to the genome of Avian Infectious Bronchitis Virus.

[18202] VGAM357 precursor RNA folds onto itself, forming VGAM357 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18203] An enzyme complex designated DICER COMPLEX, `dices` the VGAM357 folded precursor RNA into VGAM357 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM357 RNA is designated SEQ ID:3068, and is provided hereinbelow with reference to the sequence listing part.

[18204] VGAM357 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM357 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM357 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18205] VGAM357 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM357 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM357 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM357 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM357 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18206] The complementary binding of VGAM357 RNA, herein designated VGAM RNA, to host target binding sites on VGAM357 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM357 host target RNA into VGAM357 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18207] It is appreciated that VGAM357 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM357 host target genes. The mRNA of each one of this plurality of VGAM357 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM357 RNA, herein designated VGAM RNA, and which when bound by VGAM357 RNA causes inhibition of translation of respective one or more VGAM357 host target proteins.

[18208] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM357 gene, herein designated VGAM GENE, on one or more VGAM357 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-



cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18209] It is yet further appreciated that a function of VGAM357 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM357 correlate with, and may be deduced from, the identity of the host target genes which VGAM357 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18210] Nucleotide sequences of the VGAM357 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM357 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM357 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM357 are further described hereinbelow with reference to Table 1.

[18211] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM357 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM357 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18212] As mentioned hereinabove with reference to Fig. 1, a function of VGAM357 gene, herein designated VGAM is inhibition of expression of VGAM357 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM357 correlate with, and may be deduced from, the identity of the target genes which VGAM357 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18213] AAT1 (Accession XM\_087415) is a VGAM357 host target gene. AAT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AAT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-

ble 2 illustrates the complementarity of the nucleotide sequences of AAT1 BINDING SITE, designated SEQ ID:39226, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18214] A function of VGAM357 is therefore inhibition of AAT1 (Accession XM\_087415), a gene which linkage between A1BG and Lutheran blood group . Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AAT1. The function of AAT1 has been established by previous studies. The complete amino acid sequence of alpha-1B-glycoprotein, a plasma protein of unknown function, was determined by Ishioka et al. (1986). Sequence homology to immunoglobulins was recognized. Alpha-1B-glycoprotein is present in normal adult plasma at an average concentration of 22 mg/dl. Gahne et al. (1987) observed genetic polymorphism of A1B using one-dimensional horizontal polyacrylamide gel electrophoresis followed by Western blotting with specific antiserum. Three different phenotypes, designated 1-1, 1-2, and 2-2, were observed. Family data supported the hypothesis that the three phenotypes are determined by 2 codominant alleles at an autosomal locus. In pigs the homo-

gous locus is linked to malignant hyperthermia (OMIM Ref. No. 145600). Several other linkages in pigs and in horses suggest that human chromosomes 19, 6, and 1 are 'candidate chromosomes' for bearing the human A1B. Juneja et al. (1988) found a higher degree of A1B polymorphism in American blacks than in Caucasian populations. They described new alleles. Eiberg et al. (1989) reported exclusion data for localization of the alpha-1B-glycoprotein gene polymorphism. Eiberg et al. (1989) found linkage between A1BG and Lutheran blood group (OMIM Ref. No. 111150); lod = 3.06 at theta = 0.05 in males, and lod = 1.42 at theta = 0.10 in females. They suggested that the most likely order of genes on chromosome 19 is C3--SE--LU--A1BG.

[18215] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18216] Ishioka, N.; Takahashi, N.; Putnam, F. W. : Amino acid sequence of human plasma alpha-1B-glycoprotein: homology to the immunoglobulin supergene family. Proc. Nat. Acad. Sci. 83: 2363-2367, 1986. ; and

[18217] Eiberg, H.; Bisgaard, M. L.; Mohr, J. : Linkage between alpha-1-B-glycoprotein (A1BG) and Lutheran (LU) red blood

group system: assignment to chromosome 19: new genetic variants of A1BG.

[18218] Further studies establishing the function and utilities of AAT1 are found in John Hopkins OMIM database record ID 607086, and in cited publications numbered 5560–5561 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fatty-acid-Coenzyme A Ligase, Long-chain 5 (FACL5, Accession XM\_034424) is another VGAM357 host target gene. FACL5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FACL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FACL5 BINDING SITE, designated SEQ ID:32106, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18219] Another function of VGAM357 is therefore inhibition of Fatty-acid-Coenzyme A Ligase, Long-chain 5 (FACL5, Accession XM\_034424), a gene which may be involved in fatty acid metabolism; contains an AMP-binding domain. Accordingly, utilities of VGAM357 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with FACL5. The function of FACL5 has been established by previous studies. Acyl-CoA synthetase (ACS; EC 6.2.1.3) catalyzes the formation of acyl-CoA from fatty acid, ATP, and CoA. This reaction is essential in mammalian fatty acid metabolism. In addition, ACS mediates the transportation of fatty acids into cells by cooperating with the fatty acid transporter protein (FATP; 600691). Oikawa et al. (1998) cloned rat Acs5 and found that it is highly expressed in proliferating 3T3-L1 cells. By screening a liver cDNA library with rat ACS5 as the probe, Yamashita et al. (2000) isolated a cDNA encoding human ACS5. The deduced 683-amino acid protein shares approximately 80% amino acid identity with the rat sequence. Northern blot analysis detected 2 major ACS5 transcripts of 2.5 and 3.7 kb in a wide range of tissues, with highest expression in uterus and spleen. Markedly increased levels of ACS5 transcripts were detected in a glioma line and in primary gliomas of grade IV malignancy, while ACS5 expression was found to be low in normal brain. Yamashita et al. (2000) found that cultured glioma cells infected with an adenovirus encoding ACS5 displayed induced cell growth on exposure to palmitate.

Consistent with the induction of cell growth, the virus-infected cells displayed induced uptake of palmitate. These results demonstrated a novel fatty acid-induced glioma cell growth mediated by ACS5.

[18220] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18221] Oikawa, E.; Iijima, H.; Suzuki, T.; Sasano, H.; Sato, H.; Kamataki, A.; Nagura, H.; Kang, M. J.; Fujino, T.; Suzuki, H.; Yamamoto, T. T. : A novel acyl-CoA synthetase, ACS5, expressed in intestinal epithelial cells and proliferating preadipocytes. J. Biochem. 124: 679–685, 1998. ; and

[18222] Yamashita, Y.; Kumabe, T.; Cho, Y.-Y.; Watanabe, M.; Kawagishi, J.; Yoshimoto, T.; Fujino, T.; Kang, M.-J.; Yamamoto, T. T. : Fatty acid induced glioma cell growth is mediated by the a.

[18223] Further studies establishing the function and utilities of FACL5 are found in John Hopkins OMIM database record ID 605677, and in cited publications numbered 968–969 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_080921) is another VGAM357 host target gene. PT-

PTPRC BINDING SITE1 and PTPRC BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PTPRC, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPRC BINDING SITE1 and PTPRC BINDING SITE2, designated SEQ ID:28143 and SEQ ID:8717 respectively, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18224] Another function of VGAM357 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_080921). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRC. Basic Leucine Zipper and W2 Domains 1 (BZW1, Accession NM\_014670) is another VGAM357 host target gene. BZW1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BZW1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BZW1 BINDING SITE, designated SEQ ID:16127, to the nu-



cleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18225] Another function of VGAM357 is therefore inhibition of Basic Leucine Zipper and W2 Domains 1 (BZW1, Accession NM\_014670). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BZW1. Ectonucleotide Pyrophosphatase/phosphodiesterase 4 (putative function) (ENPP4, Accession NM\_014936) is another VGAM357 host target gene. ENPP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ENPP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ENPP4 BINDING SITE, designated SEQ ID:17238, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18226] Another function of VGAM357 is therefore inhibition of Ectonucleotide Pyrophosphatase/phosphodiesterase 4 (putative function) (ENPP4, Accession NM\_014936). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with ENPP4. FLJ23056 (Accession NM\_024582) is another VGAM357 host target gene. FLJ23056 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23056 BINDING SITE, designated SEQ ID:23806, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18227] Another function of VGAM357 is therefore inhibition of FLJ23056 (Accession NM\_024582). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23056. NUCKS (Accession NM\_022731) is another VGAM357 host target gene. NUCKS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUCKS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUCKS BINDING SITE, designated SEQ ID:22935, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ

ID:3068.

[18228] Another function of VGAM357 is therefore inhibition of NUCKS (Accession NM\_022731). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUCKS. TSP-NY (Accession NM\_032573) is another VGAM357 host target gene. TSP-NY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSP-NY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSP-NY BINDING SITE, designated SEQ ID:26302, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18229] Another function of VGAM357 is therefore inhibition of TSP-NY (Accession NM\_032573). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSP-NY. LOC151098 (Accession XM\_087096) is another VGAM357 host target gene. LOC151098 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151098, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151098 BINDING SITE, designated SEQ ID:39048, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18230] Another function of VGAM357 is therefore inhibition of LOC151098 (Accession XM\_087096). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151098. LOC151579 (Accession XM\_045290) is another VGAM357 host target gene. LOC151579 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151579, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151579 BINDING SITE, designated SEQ ID:34421, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18231] Another function of VGAM357 is therefore inhibition of LOC151579 (Accession XM\_045290). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC151579. LOC158476 (Accession XM\_098955) is another VGAM357 host target gene. LOC158476 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158476, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158476 BINDING SITE, designated SEQ ID:41995, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18232] Another function of VGAM357 is therefore inhibition of LOC158476 (Accession XM\_098955). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158476. LOC200982 (Accession XM\_117305) is another VGAM357 host target gene. LOC200982 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200982, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200982 BINDING SITE, designated SEQ ID:43370, to

the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18233] Another function of VGAM357 is therefore inhibition of LOC200982 (Accession XM\_117305). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200982. LOC201516 (Accession XM\_113974) is another VGAM357 host target gene. LOC201516 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC201516, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201516 BINDING SITE, designated SEQ ID:42581, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18234] Another function of VGAM357 is therefore inhibition of LOC201516 (Accession XM\_113974). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201516. LOC90593 (Accession XM\_032815) is another VGAM357 host target gene. LOC90593 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC90593, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90593 BINDING SITE, designated SEQ ID:31762, to the nucleotide sequence of VGAM357 RNA, herein designated VGAM RNA, also designated SEQ ID:3068.

[18235] Another function of VGAM357 is therefore inhibition of LOC90593 (Accession XM\_032815). Accordingly, utilities of VGAM357 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90593. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 358 (VGAM358) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18236] VGAM358 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM358 was detected is described hereinabove with reference to Figs. 1–8.

[18237] VGAM358 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM358 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18238] VGAM358 gene encodes a VGAM358 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM358 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM358 precursor RNA is designated SEQ ID:344, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:344 is located at position 10172 relative to the genome of Avian Infectious Bronchitis Virus.

[18239] VGAM358 precursor RNA folds onto itself, forming VGAM358 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.



[18240] An enzyme complex designated DICER COMPLEX, `dices` the VGAM358 folded precursor RNA into VGAM358 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM358 RNA is designated SEQ ID:3069, and is provided hereinbelow with reference to the sequence listing part.

[18241] VGAM358 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM358 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM358 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18242] VGAM358 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM358 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM358 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM358 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM358 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18243] The complementary binding of VGAM358 RNA, herein designated VGAM RNA, to host target binding sites on VGAM358 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM358 host tar–

get RNA into VGAM358 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18244] It is appreciated that VGAM358 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM358 host target genes. The mRNA of each one of this plurality of VGAM358 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM358 RNA, herein designated VGAM RNA, and which when bound by VGAM358 RNA causes inhibition of translation of respective one or more VGAM358 host target proteins.

[18245] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM358 gene, herein designated VGAM GENE, on one or more VGAM358 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18246] It is yet further appreciated that a function of VGAM358 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM358 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM358 correlate with, and may be deduced from, the identity of the host target genes which VGAM358 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18247] Nucleotide sequences of the VGAM358 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM358 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM358 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM358 are further

described hereinbelow with reference to Table 1.

[18248] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM358 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM358 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18249] As mentioned hereinabove with reference to Fig. 1, a function of VGAM358 gene, herein designated VGAM is inhibition of expression of VGAM358 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM358 correlate with, and may be deduced from, the identity of the target genes which VGAM358 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18250] DKFZp547C176 (Accession XM\_040799) is a VGAM358 host target gene. DKFZp547C176 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547C176, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DK-

FZp547C176 BINDING SITE, designated SEQ ID:33382, to the nucleotide sequence of VGAM358 RNA, herein designated VGAM RNA, also designated SEQ ID:3069.

[18251] A function of VGAM358 is therefore inhibition of DK-FZp547C176 (Accession XM\_040799). Accordingly, utilities of VGAM358 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547C176. FLJ12806 (Accession NM\_022831) is another VGAM358 host target gene. FLJ12806 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12806, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12806 BINDING SITE, designated SEQ ID:23111, to the nucleotide sequence of VGAM358 RNA, herein designated VGAM RNA, also designated SEQ ID:3069.

[18252] Another function of VGAM358 is therefore inhibition of FLJ12806 (Accession NM\_022831). Accordingly, utilities of VGAM358 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12806. LOC222160 (Accession XM\_168431) is another VGAM358 host target gene. LOC222160 BINDING SITE is HOST TAR-

GET binding site found in the 5' untranslated region of mRNA encoded by LOC222160, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222160 BINDING SITE, designated SEQ ID:45166, to the nucleotide sequence of VGAM358 RNA, herein designated VGAM RNA, also designated SEQ ID:3069.

[18253] Another function of VGAM358 is therefore inhibition of LOC222160 (Accession XM\_168431). Accordingly, utilities of VGAM358 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222160. LOC51696 (Accession NM\_016217) is another VGAM358 host target gene. LOC51696 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51696 BINDING SITE, designated SEQ ID:18304, to the nucleotide sequence of VGAM358 RNA, herein designated VGAM RNA, also designated SEQ ID:3069.

[18254] Another function of VGAM358 is therefore inhibition of

LOC51696 (Accession NM\_016217). Accordingly, utilities of VGAM358 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51696. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 359 (VGAM359) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18255] VGAM359 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM359 was detected is described hereinabove with reference to Figs. 1–8.

[18256] VGAM359 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM359 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18257] VGAM359 gene encodes a VGAM359 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM359 precursor RNA does not encode a protein. A nucleotide



sequence identical or highly similar to the nucleotide sequence of VGAM359 precursor RNA is designated SEQ ID:345, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:345 is located at position 9184 relative to the genome of Avian Infectious Bronchitis Virus.

[18258] VGAM359 precursor RNA folds onto itself, forming VGAM359 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18259] An enzyme complex designated DICER COMPLEX, `dices` the VGAM359 folded precursor RNA into VGAM359 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide se-

quence of VGAM359 RNA is designated SEQ ID:3070, and is provided hereinbelow with reference to the sequence listing part.

[18260] VGAM359 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM359 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM359 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[18261] VGAM359 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM359 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM359 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM359 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM359 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[18262] The complementary binding of VGAM359 RNA, herein designated VGAM RNA, to host target binding sites on VGAM359 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM359 host target RNA into VGAM359 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18263] It is appreciated that VGAM359 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM359 host target genes. The mRNA of each one of this plurality of VGAM359 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM359 RNA, herein designated VGAM RNA, and which when bound by VGAM359 RNA causes inhibition of translation of respective one or more VGAM359 host target proteins.

[18264] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM359 gene, herein designated VGAM GENE, on one or more VGAM359 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18265] It is yet further appreciated that a function of VGAM359 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM359 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM359 correlate with, and may be deduced from, the identity of the host target genes which VGAM359 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18266] Nucleotide sequences of the VGAM359 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM359 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM359 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM359 are further described hereinbelow with reference to Table 1.

[18267] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM359 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM359 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18268] As mentioned hereinabove with reference to Fig. 1, a function of VGAM359 gene, herein designated VGAM is inhibition of expression of VGAM359 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM359 correlate with, and may be deduced from, the identity of the target genes which VGAM359 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18269] Estrogen-related Receptor Gamma (ESRRG, Accession XM\_039053) is a VGAM359 host target gene. ESRRG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESRRG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRG BINDING SITE, designated SEQ ID:32994, to the nucleotide sequence of VGAM359 RNA, herein designated VGAM RNA, also designated SEQ ID:3070.

[18270] A function of VGAM359 is therefore inhibition of Estrogen-related Receptor Gamma (ESRRG, Accession XM\_039053), a gene which Estrogen-related receptor gamma. Accordingly, utilities of VGAM359 include diagnosis, prevention and treatment of diseases and clinical

conditions associated with ESRRG. The function of ESRRG has been established by previous studies. Members of the nuclear receptor superfamily are important regulators of development, cell proliferation, and physiology. During an analysis of the critical region of type IIa Usher syndrome (USH2A; 276901) at 1q41, Eudy et al. (1998) constructed a cDNA contig of ESRRG. Northern blot analysis detected a 5.5-kb ESRRG transcript in a variety of human adult and fetal tissues, with the highest level in fetal brain. The predicted 436-amino acid ESRRG protein, which is a member of the steroid/thyroid/retinoid receptor superfamily, is 76% identical to the orphan receptor ESRRB (OMIM Ref. No. 602167) and 63% identical to ESRRG (OMIM Ref. No. 601998). Heard et al. (2000) reported that the ESRRG mRNA is highly alternatively spliced at the 5-prime end, giving rise to a number of tissue-specific RNA species, some of which encode protein isoforms differing in the N-terminal region. Like ESRRG and ESRRB, ESRRG binds as a monomer to an ERR-alpha response element (ERRE). Hong et al. (1999) identified mouse *Esrrg*, which they called *Err3*, by yeast 2-hybrid screening using the transcriptional coactivator GRIP1 (OMIM Ref. No. 604597) as bait. The putative full-length mouse *Err3* contains 458 amino acids

and is closely related to Err1 and Err2. All ERR family members share an almost identical DNA-binding domain, which shares 68% amino acid identity with that of estrogen receptor. Expression of Err3 in adult mouse was restricted; highest expression was observed in heart, kidney, and brain. In mouse embryo, no expression was observed at day 7, and highest expression occurred around days 11 to 15. Although Err3 is more closely related to Err2 than to Err1, the expression pattern for Err3 was similar to that of Err1 and distinct from that for Err2, suggesting a unique role for Err3 in development. Eudy et al. (1998) mapped the ESRRG gene to the USH2A critical region on chromosome 1q41.

[18271] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18272] Heard, D. J.; Norby, P. L.; Holloway, J.; Vissing, H. : Human ERR-gamma, a third member of the estrogen receptor-related receptor (ERR) subfamily of orphan nuclear receptors: tissue-specific isoforms are expressed during development in the adult. *Molec. Endocr.* 14: 382-392, 2000. ; and

[18273] Eudy, J. D.; Yao, S.; Weston, M. D.; Ma-Edmonds, M.; Tal-



madge, C. B.; Cheng, J. J.; Kimberling, W. J.; Sumegi, J. : Isolation of a gene encoding a novel member of the nuclear receptor s.

[18274] Further studies establishing the function and utilities of ESRRG are found in John Hopkins OMIM database record ID 602969, and in cited publications numbered 8478–847 and 8539–8540 listed in the bibliography section herein–below, which are also hereby incorporated by reference. C1q and Tumor Necrosis Factor Related Protein 2 (C1QTNF2, Accession NM\_031908) is another VGAM359 host target gene. C1QTNF2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C1QTNF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1QTNF2 BINDING SITE, designated SEQ ID:25650, to the nucleotide sequence of VGAM359 RNA, herein designated VGAM RNA, also designated SEQ ID:3070.

[18275] Another function of VGAM359 is therefore inhibition of C1q and Tumor Necrosis Factor Related Protein 2 (C1QTNF2, Accession NM\_031908). Accordingly, utilities of VGAM359 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with C1QTNF2. FLJ32865 (Accession NM\_144613) is another VGAM359 host target gene. FLJ32865 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ32865, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32865 BINDING SITE, designated SEQ ID:29423, to the nucleotide sequence of VGAM359 RNA, herein designated VGAM RNA, also designated SEQ ID:3070.

[18276] Another function of VGAM359 is therefore inhibition of FLJ32865 (Accession NM\_144613). Accordingly, utilities of VGAM359 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32865. Junctional Adhesion Molecule 1 (JAM1, Accession NM\_144502) is another VGAM359 host target gene. JAM1 BINDING SITE1 through JAM1 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by JAM1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JAM1 BINDING SITE1

through JAM1 BINDING SITE4, designated SEQ ID:29324, SEQ ID:29344, SEQ ID:29333 and SEQ ID:18857 respectively, to the nucleotide sequence of VGAM359 RNA, herein designated VGAM RNA, also designated SEQ ID:3070.

[18277] Another function of VGAM359 is therefore inhibition of Junctional Adhesion Molecule 1 (JAM1, Accession NM\_144502). Accordingly, utilities of VGAM359 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JAM1. LOC201627 (Accession XM\_114353) is another VGAM359 host target gene. LOC201627 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201627, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201627 BINDING SITE, designated SEQ ID:42896, to the nucleotide sequence of VGAM359 RNA, herein designated VGAM RNA, also designated SEQ ID:3070.

[18278] Another function of VGAM359 is therefore inhibition of LOC201627 (Accession XM\_114353). Accordingly, utilities of VGAM359 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC201627. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 360 (VGAM360) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18279] VGAM360 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM360 was detected is described hereinabove with reference to Figs. 1–8.

[18280] VGAM360 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM360 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18281] VGAM360 gene encodes a VGAM360 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM360 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM360 precursor RNA is designated SEQ

ID:346, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:346 is located at position 11848 relative to the genome of Avian Infectious Bronchitis Virus.

[18282] VGAM360 precursor RNA folds onto itself, forming VGAM360 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18283] An enzyme complex designated DICER COMPLEX, `dices` the VGAM360 folded precursor RNA into VGAM360 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM360 RNA is designated SEQ ID:3071, and is provided hereinbelow with reference to the sequence

listing part.

[18284] VGAM360 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM360 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM360 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18285] VGAM360 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM360 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM360 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM360 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM360 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18286] The complementary binding of VGAM360 RNA, herein designated VGAM RNA, to host target binding sites on VGAM360 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM360 host target RNA into VGAM360 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18287] It is appreciated that VGAM360 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM360 host target genes. The mRNA of each one of this plurality of VGAM360 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM360 RNA, herein designated VGAM

RNA, and which when bound by VGAM360 RNA causes inhibition of translation of respective one or more VGAM360 host target proteins.

[18288] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM360 gene, herein designated VGAM GENE, on one or more VGAM360 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18289] It is yet further appreciated that a function of VGAM360 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,



utilities of VGAM360 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM360 correlate with, and may be deduced from, the identity of the host target genes which VGAM360 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18290] Nucleotide sequences of the VGAM360 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM360 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM360 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM360 are further described hereinbelow with reference to Table 1.

[18291] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM360 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM360 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18292] As mentioned hereinabove with reference to Fig. 1, a function of VGAM360 gene, herein designated VGAM is

inhibition of expression of VGAM360 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM360 correlate with, and may be deduced from, the identity of the target genes which VGAM360 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18293] Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010) is a VGAM360 host target gene. NRCAM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRCAM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRCAM BINDING SITE, designated SEQ ID:11447, to the nucleotide sequence of VGAM360 RNA, herein designated VGAM RNA, also designated SEQ ID:3071.

[18294] A function of VGAM360 is therefore inhibition of Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010), a gene which functions as a cell surface protein and belongs to the immunoglobulin superfamily. Accordingly, utilities of VGAM360 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRCAM. The function of NRCAM and its association

with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM268.UPF3A (Accession NM\_023011) is another VGAM360 host target gene. UPF3A BINDING SITE1 and UPF3A BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by UPF3A, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UPF3A BINDING SITE1 and UPF3A BINDING SITE2, designated SEQ ID:23276 and SEQ ID:27987 respectively, to the nucleotide sequence of VGAM360 RNA, herein designated VGAM RNA, also designated SEQ ID:3071.

[18295] Another function of VGAM360 is therefore inhibition of UPF3A (Accession NM\_023011), a gene which facilitates the export of spliced mRNAs by recruiting mRNA export proteins. Accordingly, utilities of VGAM360 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UPF3A. The function of UPF3A has been established by previous studies. Using comparative genomics and RACE, Serin et al. (2001) isolated cDNAs encoding UPF3A, which they called UPF3, and UPF3B,

which they called UPF3X. UPF3A encodes a 452–amino acid protein and a 420–amino acid splice variant. Northern blot analysis revealed expression of 2.1– and 2.4–kb UPF3A transcripts in HeLa cells. By immunoprecipitation and immunoblot analyses of nucleoplasmic fractions, Kim et al. (2001) showed that UPF3A and UPF3B are associated in an RNase–resistant manner with Y14 (RBM8A; 605313), as well as with the mRNA export factors ALY (OMIM Ref. No. 604171) and TAP (NXF1; 602647), in mRNA–protein complexes. UPF3 proteins appeared to bind immediately upstream of exon–exon junctions. Kim et al. (2001) concluded that UPF3 proteins facilitate the export of spliced mRNAs by recruiting mRNA export proteins. They proposed that UPF3 functions in NMD and travels with the mRNA to the cytoplasm, where a leading translating ribosome displaces the UPF3–Y14 complexes from the mRNA.

[18296] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18297] Serin, G.; Gersappe, A.; Black, J. D.; Aronoff, R.; Maquat, L. E. : Identification and characterization of human orthologues to *Saccharomyces cerevisiae* Upf2 protein and Upf3 protein (*Caenorhabditis elegans* SMG–4). *Molec. Cell. Biol.*

21: 209–223, 2001. ; and

[18298] Kim, V. N.; Kataoka, N.; Dreyfuss, G. : Role of the non-sense-mediated decay factor hUpf3 in the splicing-dependent exon-exon junction complex. Science 293: 1832–1836, 2001.

[18299] Further studies establishing the function and utilities of UPF3A are found in John Hopkins OMIM database record ID 605530, and in cited publications numbered 9142–9145 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC163882 (Accession XM\_089211) is another VGAM360 host target gene. LOC163882 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC163882, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163882 BINDING SITE, designated SEQ ID:39969, to the nucleotide sequence of VGAM360 RNA, herein designated VGAM RNA, also designated SEQ ID:3071.

[18300] Another function of VGAM360 is therefore inhibition of LOC163882 (Accession XM\_089211). Accordingly, utilities of VGAM360 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC163882. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 361 (VGAM361) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18301] VGAM361 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM361 was detected is described hereinabove with reference to Figs. 1–8.

[18302] VGAM361 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM361 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18303] VGAM361 gene encodes a VGAM361 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM361 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM361 precursor RNA is designated SEQ

ID:347, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:347 is located at position 6715 relative to the genome of Avian Infectious Bronchitis Virus.

[18304] VGAM361 precursor RNA folds onto itself, forming VGAM361 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18305] An enzyme complex designated DICER COMPLEX, `dices` the VGAM361 folded precursor RNA into VGAM361 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM361 RNA is designated SEQ ID:3072, and is provided hereinbelow with reference to the sequence

listing part.

[18306] VGAM361 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM361 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM361 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18307] VGAM361 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM361 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM361 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM361 RNA, herein designated VGAM RNA, may



have a different number of host target binding sites in untranslated regions of a VGAM361 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18308] The complementary binding of VGAM361 RNA, herein designated VGAM RNA, to host target binding sites on VGAM361 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM361 host target RNA into VGAM361 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18309] It is appreciated that VGAM361 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM361 host target genes. The mRNA of each one of this plurality of VGAM361 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM361 RNA, herein designated VGAM

RNA, and which when bound by VGAM361 RNA causes inhibition of translation of respective one or more VGAM361 host target proteins.

[18310] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM361 gene, herein designated VGAM GENE, on one or more VGAM361 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18311] It is yet further appreciated that a function of VGAM361 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM361 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM361 correlate with, and may be deduced from, the identity of the host target genes which VGAM361 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18312] Nucleotide sequences of the VGAM361 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM361 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM361 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM361 are further described hereinbelow with reference to Table 1.

[18313] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM361 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM361 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18314] As mentioned hereinabove with reference to Fig. 1, a function of VGAM361 gene, herein designated VGAM is

inhibition of expression of VGAM361 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM361 correlate with, and may be deduced from, the identity of the target genes which VGAM361 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18315] LOC149465 (Accession XM\_086543) is a VGAM361 host target gene. LOC149465 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149465 BINDING SITE, designated SEQ ID:38759, to the nucleotide sequence of VGAM361 RNA, herein designated VGAM RNA, also designated SEQ ID:3072.

[18316] A function of VGAM361 is therefore inhibition of LOC149465 (Accession XM\_086543). Accordingly, utilities of VGAM361 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149465. LOC90591 (Accession XM\_032811) is another VGAM361 host target gene. LOC90591 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC90591, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90591 BINDING SITE, designated SEQ ID:31758, to the nucleotide sequence of VGAM361 RNA, herein designated VGAM RNA, also designated SEQ ID:3072.

[18317] Another function of VGAM361 is therefore inhibition of LOC90591 (Accession XM\_032811). Accordingly, utilities of VGAM361 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90591. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 362 (VGAM362) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18318] VGAM362 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM362 was detected is described hereinabove with reference to Figs. 1–8.

[18319] VGAM362 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM362 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18320] VGAM362 gene encodes a VGAM362 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM362 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM362 precursor RNA is designated SEQ ID:348, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:348 is located at position 4697 relative to the genome of Avian Infectious Bronchitis Virus.

[18321] VGAM362 precursor RNA folds onto itself, forming VGAM362 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18322] An enzyme complex designated DICER COMPLEX, `dices` the VGAM362 folded precursor RNA into VGAM362 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM362 RNA is designated SEQ ID:3073, and is provided hereinbelow with reference to the sequence listing part.

[18323] VGAM362 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM362 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM362 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18324] VGAM362 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM362 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM362 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM362 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM362 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[18325] The complementary binding of VGAM362 RNA, herein designated VGAM RNA, to host target binding sites on VGAM362 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM362 host tar-



get RNA into VGAM362 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18326] It is appreciated that VGAM362 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM362 host target genes. The mRNA of each one of this plurality of VGAM362 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM362 RNA, herein designated VGAM RNA, and which when bound by VGAM362 RNA causes inhibition of translation of respective one or more VGAM362 host target proteins.

[18327] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM362 gene, herein designated VGAM GENE, on one or more VGAM362 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18328] It is yet further appreciated that a function of VGAM362 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM362 correlate with, and may be deduced from, the identity of the host target genes which VGAM362 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18329] Nucleotide sequences of the VGAM362 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM362 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM362 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM362 are further

described hereinbelow with reference to Table 1.

[18330] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM362 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM362 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18331] As mentioned hereinabove with reference to Fig. 1, a function of VGAM362 gene, herein designated VGAM is inhibition of expression of VGAM362 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM362 correlate with, and may be deduced from, the identity of the target genes which VGAM362 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18332] GNE (Accession NM\_005476) is a VGAM362 host target gene. GNE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GNE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GNE BINDING SITE, designated SEQ ID:11976,

to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18333] A function of VGAM362 is therefore inhibition of GNE (Accession NM\_005476), a gene which has roles in sialic acid biosynthesis and regulates cell surface sialylation. Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNE. The function of GNE has been established by previous studies. Keppler et al. (1999) determined that UDP-GlcNAc 2-epimerase activity is rate-limiting for the biosynthesis of sialic acid and is required for sialylation in hematopoietic cells. The activity of the enzyme can be controlled at the transcriptional level and can affect the sialylation and function of specific cell surface molecules expressed on B cells and myeloid cells. In a Genbank submission (AJ238764), these authors reported the sequence of a human UDP-GlcNAc 2-epimerase cDNA. Animal model experiments lend further support to the function of GNE. Schwarzkopf et al. (2002) reported that inactivation of GNE (which is bifunctional and is the key enzyme of sialic acid biosynthesis) by gene targeting in mice caused early embryonic lethality, thereby emphasizing the fundamental role of the enzyme and sialylation

during development. The need of the enzyme for a defined sialylation process is exemplified by the polysialylation of the neural cell adhesion molecule in embryonic stem cells.

[18334] It is appreciated that the abovementioned animal model for GNE is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[18335] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18336] Keppler, O. T.; Hinderlich, S.; Langner, J.; Schwartz-Albiez, R.; Reutter, W.; Pawlita, M. : UDP-GlcNAc 2-epimerase: a regulator of cell surface sialylation. Science 284: 1372-1376, 1999. ; and

[18337] Schwarzkopf, M.; Knobloch, K.-P.; Rohde, E.; Hinderlich, S.; Wiechens, N.; Lucka, L.; Horak, I.; Reutter, W.; Horstkoorte, R. : Sialylation is essential for early development in mice.

[18338] Further studies establishing the function and utilities of GNE are found in John Hopkins OMIM database record ID 603824, and in cited publications numbered 7516-5179, 7929-5181, 1662-1663, 5167-5168, 1664, 5182, 1139

and 11407 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Membrane-spanning 4-domains, Subfamily A, Member 1 (MS4A1, Accession NM\_000139) is another VGAM362 host target gene. MS4A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MS4A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MS4A1 BINDING SITE, designated SEQ ID:5631, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18339] Another function of VGAM362 is therefore inhibition of Membrane-spanning 4-domains, Subfamily A, Member 1 (MS4A1, Accession NM\_000139), a gene which may be involved in the regulation of b-cell activation and proliferation. Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MS4A1. The function of MS4A1 has been established by previous studies. B1, also known as CD20 or MS4A1, is a human B-lymphocyte surface molecule that is widely expressed during B-cell ontogeny,

from early pre-B-cell developmental stages until final differentiation into plasma cells. Functional studies using monoclonal antibodies have shown that antibody binding to B1 inhibits B-cell proliferation caused by mitogens and inhibits B-cell differentiation. Tedder et al. (1988) described the primary structure of CD20. Tedder et al. (1989) showed that the CD20 gene is 16 kb long and contains 8 exons. Using in situ hybridization and Southern blotting of hybrid cell DNA, Tedder et al. (1989) showed that the CD20 gene is located on 11q12-q13. This localization places the CD20 gene near the site of the t(11;14)(q13;q32) translocation that is found in a subgroup of B-cell malignancies; see 151400. The CD20 gene was found to lie on the centromeric side of BCL1 (OMIM Ref. No. 168461) and to be separated from BCL1 by at least 50 kb of DNA. The proximal location of CD20 was indicated by the fact that it is not translocated to chromosome 14 in the translocation. It must be located between the centromere of chromosome 11 and the 3-prime end of BCL1. Szepetowski et al. (1993) studied amplification of the BCL1 region in breast cancer to map genes in the 11q13 band. CD20 was the most proximal of 13 genes located centromeric to BCL1 and was in the same group as

CD5, PGA4 (OMIM Ref. No. 169720), and FTH1 (OMIM Ref. No. 134770). Distal to this cluster was a group of 3 genes, COX8 (OMIM Ref. No. 123870), PYGM (OMIM Ref. No. 232600), and SEA (OMIM Ref. No. 165110), of which the most proximal was COX8.

[18340] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18341] Szepetowski, P.; Perucca-Lostanlen, D.; Gaudray, P. : Mapping genes according to their amplification status in tumor cells: contribution to the map of 11q13. Genomics 16: 745–750, 1993. ; and

[18342] Tedder, T. F.; Klejman, G.; Schlossman, S. F.; Saito, H. : Structure of the gene encoding the human B lymphocyte differentiation antigen CD20 (B1). J. Immun. 142: 2560–2568, 1989.

[18343] Further studies establishing the function and utilities of MS4A1 are found in John Hopkins OMIM database record ID 112210, and in cited publications numbered 455 and 4552–4554 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362) is



another VGAM362 host target gene. TIMP3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIMP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMP3 BINDING SITE, designated SEQ ID:5935, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18344] Another function of VGAM362 is therefore inhibition of Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIMP3. Transient Receptor Potential Cation Channel, Subfamily C, Member 5 (TRPC5, Accession NM\_012471) is another VGAM362 host target gene. TRPC5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPC5 BINDING SITE, designated SEQ

ID:14851, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18345] Another function of VGAM362 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily C, Member 5 (TRPC5, Accession NM\_012471). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPC5. FLJ10511 (Accession NM\_018120) is another VGAM362 host target gene. FLJ10511 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10511, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10511 BINDING SITE, designated SEQ ID:19900, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18346] Another function of VGAM362 is therefore inhibition of FLJ10511 (Accession NM\_018120). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10511. IL-17RE (Accession NM\_144640) is another VGAM362

host target gene. IL-17RE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL-17RE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL-17RE BINDING SITE, designated SEQ ID:29465, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18347] Another function of VGAM362 is therefore inhibition of IL-17RE (Accession NM\_144640). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL-17RE. LOC150848 (Accession XM\_097959) is another VGAM362 host target gene. LOC150848 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150848 BINDING SITE, designated SEQ ID:41258, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18348] Another function of VGAM362 is therefore inhibition of LOC150848 (Accession XM\_097959). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150848. LOC253868 (Accession XM\_170975) is another VGAM362 host target gene. LOC253868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253868 BINDING SITE, designated SEQ ID:45746, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18349] Another function of VGAM362 is therefore inhibition of LOC253868 (Accession XM\_170975). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253868. LOC257465 (Accession XM\_088384) is another VGAM362 host target gene. LOC257465 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257465, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257465 BINDING SITE, designated SEQ ID:39667, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18350] Another function of VGAM362 is therefore inhibition of LOC257465 (Accession XM\_088384). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257465. LOC93206 (Accession XM\_049838) is another VGAM362 host target gene. LOC93206 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93206, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93206 BINDING SITE, designated SEQ ID:35519, to the nucleotide sequence of VGAM362 RNA, herein designated VGAM RNA, also designated SEQ ID:3073.

[18351] Another function of VGAM362 is therefore inhibition of LOC93206 (Accession XM\_049838). Accordingly, utilities of VGAM362 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC93206. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 363 (VGAM363) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18352] VGAM363 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM363 was detected is described hereinabove with reference to Figs. 1–8.

[18353] VGAM363 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM363 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18354] VGAM363 gene encodes a VGAM363 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM363 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM363 precursor RNA is designated SEQ ID:349, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:349 is located at position 5806 relative to the genome of Avian Infectious Bronchitis Virus.

[18355] VGAM363 precursor RNA folds onto itself, forming VGAM363 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18356] An enzyme complex designated DICER COMPLEX, `dices` the VGAM363 folded precursor RNA into VGAM363 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM363 RNA is designated SEQ ID:3074, and is provided hereinbelow with reference to the sequence listing part.

[18357] VGAM363 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM363 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM363 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.



[18358] VGAM363 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM363 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM363 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM363 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM363 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18359] The complementary binding of VGAM363 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM363 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM363 host target RNA into VGAM363 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18360] It is appreciated that VGAM363 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM363 host target genes. The mRNA of each one of this plurality of VGAM363 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM363 RNA, herein designated VGAM RNA, and which when bound by VGAM363 RNA causes inhibition of translation of respective one or more VGAM363 host target proteins.

[18361] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM363 gene, herein designated VGAM GENE, on one or more VGAM363 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18362] It is yet further appreciated that a function of VGAM363 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM363 correlate with, and may be deduced from, the identity of the host target genes which VGAM363 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18363] Nucleotide sequences of the VGAM363 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

5' duced 5' VGAM363 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM363 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM363 are further described hereinbelow with reference to Table 1.

[18364] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM363 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM363 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18365] As mentioned hereinabove with reference to Fig. 1, a function of VGAM363 gene, herein designated VGAM is inhibition of expression of VGAM363 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM363 correlate with, and may be deduced from, the identity of the target genes which VGAM363 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18366] EGF-like-domain, Multiple 5 (EGFL5, Accession XM\_098838) is a VGAM363 host target gene. EGFL5 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by EGFL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGFL5 BINDING SITE, designated SEQ ID:41874, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18367] A function of VGAM363 is therefore inhibition of EGF-like-domain, Multiple 5 (EGFL5, Accession XM\_098838). Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGFL5. Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540) is another VGAM363 host target gene. ODF2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ODF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ODF2 BINDING SITE, designated SEQ ID:8384, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18368] Another function of VGAM363 is therefore inhibition of

Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540), a gene which is very strongly similar to rat Odf2 . Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ODF2. The function of ODF2 has been established by previous studies. See ODF1 (OMIM Ref. No. 182878). Brohmann et al. (1997) used antibodies against Odf proteins to screen a rat testis expression library and isolated the rat Odf2 gene. Sequence analysis revealed that the protein has an overall alpha-helical structure with 2 regions identical to the dimerization region of a leucine zipper motif. Brohmann et al. (1997) documented Odf2 cDNAs with 3 different 5-prime end sequences, presumed to be the result of alternative splicing. They found expression of the rat gene only in testis. The EST database contains several human cDNA sequences which are closely related to rat Odf2, suggesting that a human homolog exists (Scott, 1997). These human cDNA sequences were derived from testis, epididymis, and fetal brain libraries. Shao et al. (1997) used a yeast 2-hybrid screening with the leucine zipper region of ODF1 (ODF27; Shao and van der Hoorn, 1996) as bait to isolate rat testis-specific proteins that could interact with ODF27.

They demonstrated that one of the novel genes isolated encoded the 84-kD ODF protein ODF2.

[18369] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18370] Brohmann, H.; Pinnecke, S.; Hoyer-Fender, S. : Identification and characterization of new cDNAs encoding outer dense fiber proteins of rat sperm. J. Biol. Chem. 272: 10327–10332, 1997. ; and

[18371] Shao, X.; Tarnasky, H. A.; Schalles, U.; Oko, R.; van der Hoorn, F. A. : Interactional cloning of the 84-kDa major outer dense fiber protein Odf84: leucine zippers mediate associations.

[18372] Further studies establishing the function and utilities of ODF2 are found in John Hopkins OMIM database record ID 602015, and in cited publications numbered 5928–593 and 5706–5707 listed in the bibliography section herein–below, which are also hereby incorporated by reference. Testis Derived Transcript (3 LIM domains) (TES, Accession XM\_050430) is another VGAM363 host target gene. TES BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TES, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TES BINDING SITE, designated SEQ ID:35631, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18373] Another function of VGAM363 is therefore inhibition of Testis Derived Transcript (3 LIM domains) (TES, Accession XM\_050430), a gene which acts as a tumor suppressor. Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TES. The function of TES has been established by previous studies. By construction and sequencing of a BAC contig within the FRA7G region at 7q31.2, Tatarelli et al. (2000) identified a novel gene which they called TESTIN because of its homology to mouse testin. They isolated 3 human isoforms. Isoforms 1 and 2, which use exon 1a and differ in their 3-prime UTR, contain 7 exons and encode a deduced 421-amino acid protein with a calculated molecular mass of 48 kD. Isoform 3, which uses exon 1b, encodes a deduced 412-amino acid protein with a calculated molecular mass of 47 kD. Each of the isoforms contains 3 LIM domains in the C terminus and shows 89% and 35% sequence identity with the mouse and



C. elegans homologs, respectively. Human TESTIN contains 7 putative functional sites: 4 phosphorylation sites, a glycosylation site, a myristylation site, and a cytochrome C heme-binding site. Northern blot analysis of normal human tissues demonstrated ubiquitous expression of an approximately 2.8-kb TESTIN transcript, which apparently corresponded to isoforms 2 and 3. An approximately 1.5-kb transcript, corresponding to isoform 1, was expressed at significantly higher levels in testis than in other tissues. FRA7G is a common aphidicolin-inducible fragile site at 7q31.2 showing loss of heterozygosity in human malignancies. Tatarelli et al. (2000) noted that a relationship between LIM proteins and cancer had been observed in several studies. By RT-PCR analysis, they found lack of TESTIN expression in 22% of cancer cell lines and 44% of the cell lines derived from hematologic malignancies. They determined that in most of these cases the inactivation of TESTIN expression was due to methylation of a CpG island. Analysis of the TESTIN coding region in 26 tumor cell lines revealed 3 missense mutations. The authors thus suggested that TESTIN may represent a tumor suppressor gene. Tobias et al. (2001) also cloned and characterized human TESTIN, which they called TES. Mutation

analysis of the coding TES exons in 21 human-derived cell lines revealed the presence of a frameshift mutation in 1 allele in a breast cancer cell line. Methylation of the CpG island at the 5-prime end of TES appeared to be a remarkably frequent finding, occurring in 7 of 10 ovarian carcinomas and in each of 30 tumor-derived cell lines tested. Moreover, forced expression of TES in HeLa or OV-CAR5 cells resulted in a profound reduction in growth potential, as determined by the colony formation assay. Tobias et al. (2001) suggested that TES is a tumor suppressor gene that is inactivated primarily by transcriptional silencing resulting from CpG island methylation.

[18374] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18375] Tatarelli, C.; Linnenbach, A.; Mimori, K.; Croce, C. M. : Characterization of the human TESTIN gene localized in the FRA7G region at 7q31.2. Genomics 68: 1-12, 2000. ; and

[18376] Tobias, E. S.; Hurlstone, A. F. L.; MacKenzie, E.; McFarlane, R.; Black, D. M. : The TES gene at 7q31.1 is methylated in tumours and encodes a novel growth-suppressing LIM domain prote.

[18377] Further studies establishing the function and utilities of TES are found in John Hopkins OMIM database record ID 606085, and in cited publications numbered 6120–6121 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tropomodulin 3 (ubiquitous) (TMOD3, Accession NM\_014547) is another VGAM363 host target gene. TMOD3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMOD3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMOD3 BINDING SITE, designated SEQ ID:15857, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18378] Another function of VGAM363 is therefore inhibition of Tropomodulin 3 (ubiquitous) (TMOD3, Accession NM\_014547). Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMOD3. CNIL (Accession NM\_005776) is another VGAM363 host target gene. CNIL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNIL, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNIL BINDING SITE, designated SEQ ID:12355, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18379] Another function of VGAM363 is therefore inhibition of CNIL (Accession NM\_005776). Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNIL. DKFZP564I0422 (Accession NM\_031435) is another VGAM363 host target gene. DKFZP564I0422 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564I0422, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564I0422 BINDING SITE, designated SEQ ID:25431, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18380] Another function of VGAM363 is therefore inhibition of DKFZP564I0422 (Accession NM\_031435). Accordingly, utilities of VGAM363 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with DKFZP564I0422. HT014 (Accession NM\_020362) is another VGAM363 host target gene. HT014 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HT014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HT014 BINDING SITE, designated SEQ ID:21634, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18381] Another function of VGAM363 is therefore inhibition of HT014 (Accession NM\_020362). Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HT014. KIAA0193 (Accession NM\_014766) is another VGAM363 host target gene. KIAA0193 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0193, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0193 BINDING SITE, designated SEQ ID:16540, to the nucleotide sequence of

VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18382] Another function of VGAM363 is therefore inhibition of KIAA0193 (Accession NM\_014766). Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0193. KIAA0276 (Accession XM\_048199) is another VGAM363 host target gene. KIAA0276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0276 BINDING SITE, designated SEQ ID:35135, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18383] Another function of VGAM363 is therefore inhibition of KIAA0276 (Accession XM\_048199). Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0276. LOC115073 (Accession XM\_055193) is another VGAM363 host target gene. LOC115073 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by LOC115073, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115073 BINDING SITE, designated SEQ ID:36237, to the nucleotide sequence of VGAM363 RNA, herein designated VGAM RNA, also designated SEQ ID:3074.

[18384] Another function of VGAM363 is therefore inhibition of LOC115073 (Accession XM\_055193). Accordingly, utilities of VGAM363 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115073. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 364 (VGAM364) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18385] VGAM364 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM364 was detected is described hereinabove with reference to Figs. 1–8.

[18386] VGAM364 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM364 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18387] VGAM364 gene encodes a VGAM364 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM364 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM364 precursor RNA is designated SEQ ID:350, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:350 is located at position 10866 relative to the genome of Avian Infectious Bronchitis Virus.

[18388] VGAM364 precursor RNA folds onto itself, forming VGAM364 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.



[18389] An enzyme complex designated DICER COMPLEX, `dices` the VGAM364 folded precursor RNA into VGAM364 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 53%) nucleotide sequence of VGAM364 RNA is designated SEQ ID:3075, and is provided hereinbelow with reference to the sequence listing part.

[18390] VGAM364 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM364 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM364 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18391] VGAM364 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM364 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM364 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM364 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM364 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18392] The complementary binding of VGAM364 RNA, herein designated VGAM RNA, to host target binding sites on VGAM364 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM364 host tar-

get RNA into VGAM364 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18393] It is appreciated that VGAM364 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM364 host target genes. The mRNA of each one of this plurality of VGAM364 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM364 RNA, herein designated VGAM RNA, and which when bound by VGAM364 RNA causes inhibition of translation of respective one or more VGAM364 host target proteins.

[18394] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM364 gene, herein designated VGAM GENE, on one or more VGAM364 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18395] It is yet further appreciated that a function of VGAM364 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM364 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM364 correlate with, and may be deduced from, the identity of the host target genes which VGAM364 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18396] Nucleotide sequences of the VGAM364 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM364 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM364 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM364 are further

described hereinbelow with reference to Table 1.

[18397] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM364 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM364 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18398] As mentioned hereinabove with reference to Fig. 1, a function of VGAM364 gene, herein designated VGAM is inhibition of expression of VGAM364 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM364 correlate with, and may be deduced from, the identity of the target genes which VGAM364 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18399] PSR (Accession XM\_036784) is a VGAM364 host target gene. PSR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSR BINDING SITE, designated SEQ ID:32503,

to the nucleotide sequence of VGAM364 RNA, herein designated VGAM RNA, also designated SEQ ID:3075.

[18400] A function of VGAM364 is therefore inhibition of PSR (Accession XM\_036784). Accordingly, utilities of VGAM364 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSR. Retinoic Acid Induced 17 (RAI17, Accession XM\_166091) is another VGAM364 host target gene. RAI17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAI17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAI17 BINDING SITE, designated SEQ ID:43859, to the nucleotide sequence of VGAM364 RNA, herein designated VGAM RNA, also designated SEQ ID:3075.

[18401] Another function of VGAM364 is therefore inhibition of Retinoic Acid Induced 17 (RAI17, Accession XM\_166091). Accordingly, utilities of VGAM364 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAI17. SEC24 Related Gene Family, Member A (*S. cerevisiae*) (SEC24A, Accession XM\_094581) is another VGAM364 host target gene. SEC24A BINDING SITE

is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SEC24A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC24A BINDING SITE, designated SEQ ID:40233, to the nucleotide sequence of VGAM364 RNA, herein designated VGAM RNA, also designated SEQ ID:3075.

[18402] Another function of VGAM364 is therefore inhibition of SEC24 Related Gene Family, Member A (*S. cerevisiae*) (SEC24A, Accession XM\_094581). Accordingly, utilities of VGAM364 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEC24A. LOC255565 (Accession XM\_170811) is another VGAM364 host target gene. LOC255565 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC255565, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255565 BINDING SITE, designated SEQ ID:45589, to the nucleotide sequence of VGAM364 RNA, herein designated VGAM RNA, also designated SEQ ID:3075.

[18403] Another function of VGAM364 is therefore inhibition of LOC255565 (Accession XM\_170811). Accordingly, utilities of VGAM364 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255565. LOC256512 (Accession XM\_171470) is another VGAM364 host target gene. LOC256512 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC256512, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256512 BINDING SITE, designated SEQ ID:46047, to the nucleotide sequence of VGAM364 RNA, herein designated VGAM RNA, also designated SEQ ID:3075.

[18404] Another function of VGAM364 is therefore inhibition of LOC256512 (Accession XM\_171470). Accordingly, utilities of VGAM364 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256512. LOC93166 (Accession XM\_049619) is another VGAM364 host target gene. LOC93166 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC93166, corresponding to a HOST TARGET binding site such as BINDING



SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93166 BINDING SITE, designated SEQ ID:35459, to the nucleotide sequence of VGAM364 RNA, herein designated VGAM RNA, also designated SEQ ID:3075.

[18405] Another function of VGAM364 is therefore inhibition of LOC93166 (Accession XM\_049619). Accordingly, utilities of VGAM364 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93166. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 365 (VGAM365) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18406] VGAM365 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM365 was detected is described hereinabove with reference to Figs. 1–8.

[18407] VGAM365 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM365 host target gene, herein designated

VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18408] VGAM365 gene encodes a VGAM365 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM365 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM365 precursor RNA is designated SEQ ID:351, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:351 is located at position 21704 relative to the genome of Avian Infectious Bronchitis Virus.

[18409] VGAM365 precursor RNA folds onto itself, forming VGAM365 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18410] An enzyme complex designated DICER COMPLEX, `dices` the VGAM365 folded precursor RNA into VGAM365 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM365 RNA is designated SEQ ID:3076, and is provided hereinbelow with reference to the sequence listing part.

[18411] VGAM365 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM365 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM365 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18412] VGAM365 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM365 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM365 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM365 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM365 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18413] The complementary binding of VGAM365 RNA, herein designated VGAM RNA, to host target binding sites on VGAM365 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM365 host target RNA into VGAM365 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[18414] It is appreciated that VGAM365 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM365 host target genes. The mRNA of each one of this plurality of VGAM365 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM365 RNA, herein designated VGAM RNA, and which when bound by VGAM365 RNA causes inhibition of translation of respective one or more VGAM365 host target proteins.

[18415] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM365 gene, herein designated VGAM GENE, on one or more VGAM365 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18416] It is yet further appreciated that a function of VGAM365 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM365 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM365 correlate with, and may be deduced from, the identity of the host target genes which VGAM365 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18417] Nucleotide sequences of the VGAM365 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM365 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM365 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM365 are further described hereinbelow with reference to Table 1.

[18418] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM365 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM365 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18419] As mentioned hereinabove with reference to Fig. 1, a function of VGAM365 gene, herein designated VGAM is inhibition of expression of VGAM365 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM365 correlate with, and may be deduced from, the identity of the target genes which VGAM365 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18420] Chromosome 20 Open Reading Frame 21 (C20orf21, Accession NM\_017798) is a VGAM365 host target gene. C20orf21 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf21, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf21 BINDING SITE, designated SEQ ID:19442, to the nucleotide sequence of VGAM365 RNA,

herein designated VGAM RNA, also designated SEQ ID:3076.

[18421] A function of VGAM365 is therefore inhibition of Chromosome 20 Open Reading Frame 21 (C20orf21, Accession NM\_017798). Accordingly, utilities of VGAM365 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf21. G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_014776) is another VGAM365 host target gene. GIT2 BINDING SITE1 through GIT2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GIT2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GIT2 BINDING SITE1 through GIT2 BINDING SITE3, designated SEQ ID:16595, SEQ ID:27677 and SEQ ID:27690 respectively, to the nucleotide sequence of VGAM365 RNA, herein designated VGAM RNA, also designated SEQ ID:3076.

[18422] Another function of VGAM365 is therefore inhibition of G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_014776). Accordingly, utilities of VGAM365 include diagnosis, prevention and treatment of diseases



and clinical conditions associated with GIT2. MO25 (Accession NM\_016289) is another VGAM365 host target gene. MO25 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MO25, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MO25 BINDING SITE, designated SEQ ID:18412, to the nucleotide sequence of VGAM365 RNA, herein designated VGAM RNA, also designated SEQ ID:3076.

[18423] Another function of VGAM365 is therefore inhibition of MO25 (Accession NM\_016289). Accordingly, utilities of VGAM365 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MO25. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 366 (VGAM366) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18424] VGAM366 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM366 was detected is described hereinabove with reference to Figs. 1–8.

[18425] VGAM366 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM366 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18426] VGAM366 gene encodes a VGAM366 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM366 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM366 precursor RNA is designated SEQ ID:352, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:352 is located at position 23096 relative to the genome of Avian Infectious Bronchitis Virus.

[18427] VGAM366 precursor RNA folds onto itself, forming VGAM366 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18428] An enzyme complex designated DICER COMPLEX, `dices` the VGAM366 folded precursor RNA into VGAM366 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM366 RNA is designated SEQ ID:3077, and is provided hereinbelow with reference to the sequence listing part.

[18429] VGAM366 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM366 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM366 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18430] VGAM366 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM366 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM366 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM366 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM366 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[18431] The complementary binding of VGAM366 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM366 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM366 host target RNA into VGAM366 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18432] It is appreciated that VGAM366 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM366 host target genes. The mRNA of each one of this plurality of VGAM366 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM366 RNA, herein designated VGAM RNA, and which when bound by VGAM366 RNA causes inhibition of translation of respective one or more VGAM366 host target proteins.

[18433] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM366 gene, herein designated VGAM GENE, on one or more VGAM366 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18434] It is yet further appreciated that a function of VGAM366 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM366 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM366 correlate with, and may be deduced from, the identity of the host target genes which VGAM366 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18435] Nucleotide sequences of the VGAM366 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM366 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM366 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM366 are further described hereinbelow with reference to Table 1.

[18436] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM366 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM366 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18437] As mentioned hereinabove with reference to Fig. 1, a function of VGAM366 gene, herein designated VGAM is inhibition of expression of VGAM366 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM366 correlate with, and may be deduced from, the identity of the target genes which VGAM366 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18438] Secretory Carrier Membrane Protein 1 (SCAMP1, Accession NM\_004866) is a VGAM366 host target gene. SCAMP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCAMP1,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCAMP1 BINDING SITE, designated SEQ ID:11291, to the nucleotide sequence of VGAM366 RNA, herein designated VGAM RNA, also designated SEQ ID:3077.

[18439] A function of VGAM366 is therefore inhibition of Secretory Carrier Membrane Protein 1 (SCAMP1, Accession NM\_004866), a gene which functions in post-golgi recycling pathways and acts as a recycling carrier to the cell surface. Accordingly, utilities of VGAM366 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCAMP1. The function of SCAMP1 has been established by previous studies. Brand and Castle (1993) cloned SCAMP1, which they called SCAMP37, from a rat brain cDNA library. By screening a HeLa cell cDNA library with the rat cDNA as probe, Singleton et al. (1997) cloned human SCAMP1. They also identified 2 other paralogs, SCAMP2 (OMIM Ref. No. 606912) and SCAMP3 (OMIM Ref. No. 606913), from the HeLa cell library. SCAMP1 encodes a deduced 338-amino acid protein with a calculated molecular mass of 38 kD. The pro-



tein shares structural features with SCAMP2 and SCAMP3, including a leucine zipper-like segment, a proline-rich element, an extended central core that includes 4 putative transmembrane domains, a polar segment, and an alanine-rich C terminus. SCAMP1 shares 54% and 57% overall sequence identity with SCAMP2 and SCAMP3, respectively, and 98% identity with the rat homolog. The most divergent regions are in the N terminus. Northern blot analysis detected a 3.3-kb SCAMP1 transcript in all tissues examined, with highest expression in heart, brain, skeletal muscle, and pancreas, intermediate levels in placenta and liver, and low expression in lung and kidney. Immunofluorescent localization in HeLa cells showed punctate staining enriched in the perinuclear compartment and partial colocalization with SCAMP2 and SCAMP3.

[18440] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18441] Brand, S. H.; Castle, J. D. : SCAMP-37, a new marker within the general cell surface recycling system. EMBO J. 12: 3753-3761, 1993. ; and

[18442] Singleton, D. R.; Wu, T. T.; Castle, J. D. : Three mammalian SCAMPs (secretory carrier membrane proteins) are highly

related products of distinct genes having similar subcellular distrib.

[18443] Further studies establishing the function and utilities of SCAMP1 are found in John Hopkins OMIM database record ID 606911, and in cited publications numbered 513 and 8801 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698) is another VGAM366 host target gene. BLCAP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BLCAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLCAP BINDING SITE, designated SEQ ID:13521, to the nucleotide sequence of VGAM366 RNA, herein designated VGAM RNA, also designated SEQ ID:3077.

[18444] Another function of VGAM366 is therefore inhibition of Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698). Accordingly, utilities of VGAM366 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLCAP. Chromosome 20 Open Reading Frame 108 (C20orf108, Accession

NM\_080821) is another VGAM366 host target gene.

C20orf108 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C20orf108, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf108 BINDING SITE, designated SEQ ID:28082, to the nucleotide sequence of VGAM366 RNA, herein designated VGAM RNA, also designated SEQ ID:3077.

[18445] Another function of VGAM366 is therefore inhibition of Chromosome 20 Open Reading Frame 108 (C20orf108, Accession NM\_080821). Accordingly, utilities of VGAM366 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf108.

FLJ32332 (Accession NM\_144641) is another VGAM366 host target gene. FLJ32332 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ32332, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32332 BINDING SITE, designated SEQ ID:29467, to the nucleotide sequence of

VGAM366 RNA, herein designated VGAM RNA, also designated SEQ ID:3077.

[18446] Another function of VGAM366 is therefore inhibition of FLJ32332 (Accession NM\_144641). Accordingly, utilities of VGAM366 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32332. KIAA0350 (Accession XM\_028332) is another VGAM366 host target gene. KIAA0350 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0350 BINDING SITE, designated SEQ ID:30662, to the nucleotide sequence of VGAM366 RNA, herein designated VGAM RNA, also designated SEQ ID:3077.

[18447] Another function of VGAM366 is therefore inhibition of KIAA0350 (Accession XM\_028332). Accordingly, utilities of VGAM366 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0350. KIAA0515 (Accession XM\_033380) is another VGAM366 host target gene. KIAA0515 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA0515, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0515 BINDING SITE, designated SEQ ID:31921, to the nucleotide sequence of VGAM366 RNA, herein designated VGAM RNA, also designated SEQ ID:3077.

[18448] Another function of VGAM366 is therefore inhibition of KIAA0515 (Accession XM\_033380). Accordingly, utilities of VGAM366 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0515. LOC221405 (Accession XM\_168138) is another VGAM366 host target gene. LOC221405 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221405, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221405 BINDING SITE, designated SEQ ID:45067, to the nucleotide sequence of VGAM366 RNA, herein designated VGAM RNA, also designated SEQ ID:3077.

[18449] Another function of VGAM366 is therefore inhibition of LOC221405 (Accession XM\_168138). Accordingly, utilities

of VGAM366 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221405. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 367 (VGAM367) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18450] VGAM367 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM367 was detected is described hereinabove with reference to Figs. 1–8.

[18451] VGAM367 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM367 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18452] VGAM367 gene encodes a VGAM367 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM367 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM367 precursor RNA is designated SEQ ID:353, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:353 is located at position 22094 relative to the genome of Avian Infectious Bronchitis Virus.

[18453] VGAM367 precursor RNA folds onto itself, forming VGAM367 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18454] An enzyme complex designated DICER COMPLEX, `dices` the VGAM367 folded precursor RNA into VGAM367 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM367 RNA is designated SEQ ID:3078, and

is provided hereinbelow with reference to the sequence listing part.

[18455] VGAM367 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM367 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM367 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18456] VGAM367 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM367 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM367 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-



ing – VGAM367 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM367 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18457] The complementary binding of VGAM367 RNA, herein designated VGAM RNA, to host target binding sites on VGAM367 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM367 host target RNA into VGAM367 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18458] It is appreciated that VGAM367 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM367 host target genes. The mRNA of each one of this plurality of VGAM367 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM367 RNA, herein designated VGAM RNA, and which when bound by VGAM367 RNA causes inhibition of translation of respective one or more VGAM367 host target proteins.

[18459] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM367 gene, herein designated VGAM GENE, on one or more VGAM367 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18460] It is yet further appreciated that a function of VGAM367 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM367 correlate with, and may be deduced from, the identity of the host target genes which VGAM367 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18461] Nucleotide sequences of the VGAM367 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM367 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM367 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM367 are further described hereinbelow with reference to Table 1.

[18462] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM367 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM367 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18463] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM367 gene, herein designated VGAM is inhibition of expression of VGAM367 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM367 correlate with, and may be deduced from, the identity of the target genes which VGAM367 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18464] Cyclin F (CCNF, Accession NM\_001761) is a VGAM367 host target gene. CCNF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CCNF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CCNF BINDING SITE, designated SEQ ID:7525, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18465] A function of VGAM367 is therefore inhibition of Cyclin F (CCNF, Accession NM\_001761), a gene which likely to be involved in the control of the cell cycle during s phase and g2. Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CCNF. The function of CCNF has

been established by previous studies. While searching in the 16p13.3 region for candidate genes for autosomal dominant polycystic kidney disease (PKD1; 173900), Kraus et al. (1994) identified a new member of the cyclin family. They characterized the transcript by sequencing, determination of exon/intron boundaries, and Northern blot analysis. Cyclin F is related to cyclins A (CCNA; 123835) and B (CCNB; 123836) by sequence, but its function is unknown. Cyclin F is the largest known human cyclin. Obermayr et al. (1995) mapped the gene to mouse chromosome 17 by analysis of hamster/mouse or human/mouse somatic cell hybrids containing Robertsonian translocations. For more accurate mapping, they used the BXD recombinant inbred strain system. Bai et al. (1996) determined that SKP1 (OMIM Ref. No. 601434) binds to CCNF, SKP2 (OMIM Ref. No. 601436), and potentially to other regulatory proteins that may be involved in ubiquitin proteolysis. Binding occurs through a novel motif, termed the F box. The F box contains about 40 residues and, in approximately half of the F-box proteins identified by Bai et al. (1996), it was associated with leucine-rich regions (LRRs), as in SKP2, or with WD40 repeats, as in BTRC (OMIM Ref. No. 603482). The F-box only proteins, including CCNF, contain no other

recognizable motifs.

[18466] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18467] Kraus, B.; Pohlschmidt, M.; Leung, A. L. S.; Germino, G. G.; Snarey, A.; Schneider, M. C.; Reeders, S. T.; Frischauf, A.-M. : A novel cyclin gene (CCNF) in the region of the polycystic kidney disease gene (PKD1). Genomics 24: 27-33, 1994. ; and

[18468] Bai, C.; Sen, P.; Hofmann, K.; Ma, L.; Goebel, M.; Harper, J. W.; Elledge, S. J. : SKP1 connects cell cycle regulators to the ubiquitin proteolysis machinery through a novel motif, the F-.

[18469] Further studies establishing the function and utilities of CCNF are found in John Hopkins OMIM database record ID 600227, and in cited publications numbered 7551-7553 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Disrupted In Renal Carcinoma 1 (DIRC1, Accession NM\_052952) is another VGAM367 host target gene. DIRC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DIRC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DIRC1 BINDING SITE, designated SEQ ID:27508, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18470] Another function of VGAM367 is therefore inhibition of Disrupted In Renal Carcinoma 1 (DIRC1, Accession NM\_052952), a gene which disrupted in renal carcinoma. Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIRC1. The function of DIRC1 has been established by previous studies. Podolski et al. (2001) described a reciprocal, balanced, constitutional chromosome translocation, t(2;3)(q33;q21), that is associated with familial clear cell renal cancer. By standard positional cloning strategies, Druck et al. (2001) isolated a gene disrupted by the chromosome 2 breakpoint. The gene, designated DIRC1 (disrupted in renal cancer-1), was disrupted between exons 1 and 2 by the familial translocation. The 1.5-kb DIRC1 mRNA encoded an 11-kD predicted protein of 104 amino acids. RT-PCR analysis detected low-level expression of DIRC1 in adult placenta, testis, ovary, and prostate, and in fetal kidney, spleen, and

skeletal muscle. Two familial tumors showed loss of the derivative chromosome 3, as observed in a Dutch kindred with t(2;3)-associated renal cancers in a Dutch family; see 602773. Druck et al. (2001) concluded that further studies were necessary to determine if inactivation of the DIRC1 gene contributes to the development of familial cancers.

[18471] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18472] Druck, T.; Podolski, J.; Byrski, T.; Wyrwicz, L.; Zajaczek, S.; Kata, G.; Borowka, A.; Lubinski, J.; Huebner, K. : The DIRC1 gene at chromosome 2q33 spans a familial RCC-associated t(2;3)(q33;q21) chromosome translocation. J. Hum. Genet. 46: 583–589, 2001. ; and

[18473] Podolski, J.; Zajaczek, S.; Byrski, T.; Druck, T.; Zimonjic, D. B.; Popescu, N. C.; Lubinski, J.; Huebner, K. : Characterization of a familial RCC-associated t(2;3)(q33;q21) chromosome.

[18474] Further studies establishing the function and utilities of DIRC1 are found in John Hopkins OMIM database record ID 606423, and in cited publications numbered 4541–4542 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer–



ence.KIAA0022 (Accession NM\_014880) is another VGAM367 host target gene. KIAA0022 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0022, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0022 BINDING SITE, designated SEQ ID:17028, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18475] Another function of VGAM367 is therefore inhibition of KIAA0022 (Accession NM\_014880). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0022. KIAA0265 (Accession XM\_045954) is another VGAM367 host target gene. KIAA0265 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0265, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0265 BINDING SITE, designated SEQ ID:34625, to the nucleotide sequence of VGAM367 RNA, herein designated

VGAM RNA, also designated SEQ ID:3078.

[18476] Another function of VGAM367 is therefore inhibition of KIAA0265 (Accession XM\_045954). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0265. KIAA0352 (Accession NM\_014830) is another VGAM367 host target gene. KIAA0352 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0352, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0352 BINDING SITE, designated SEQ ID:16822, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18477] Another function of VGAM367 is therefore inhibition of KIAA0352 (Accession NM\_014830). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0352. KIAA1040 (Accession XM\_051091) is another VGAM367 host target gene. KIAA1040 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1040, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1040 BINDING SITE, designated SEQ ID:35744, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18478] Another function of VGAM367 is therefore inhibition of KIAA1040 (Accession XM\_051091). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1040. KIAA1093 (Accession XM\_039385) is another VGAM367 host target gene. KIAA1093 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1093, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1093 BINDING SITE, designated SEQ ID:33064, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18479] Another function of VGAM367 is therefore inhibition of KIAA1093 (Accession XM\_039385). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1093. PFTAIRE Protein Kinase 1 (PFTK1, Accession NM\_012395) is another VGAM367 host target gene. PFTK1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PFTK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PFTK1 BINDING SITE, designated SEQ ID:14754, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18480] Another function of VGAM367 is therefore inhibition of PFTAIRE Protein Kinase 1 (PFTK1, Accession NM\_012395). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PFTK1. LOC150468 (Accession XM\_086926) is another VGAM367 host target gene. LOC150468 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC150468, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150468 BINDING SITE, desig-

nated SEQ ID:38975, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18481] Another function of VGAM367 is therefore inhibition of LOC150468 (Accession XM\_086926). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150468. LOC158314 (Accession XM\_098920) is another VGAM367 host target gene. LOC158314 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158314, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158314 BINDING SITE, designated SEQ ID:41954, to the nucleotide sequence of VGAM367 RNA, herein designated VGAM RNA, also designated SEQ ID:3078.

[18482] Another function of VGAM367 is therefore inhibition of LOC158314 (Accession XM\_098920). Accordingly, utilities of VGAM367 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158314. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 368 (VGAM368) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18483] VGAM368 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM368 was detected is described hereinabove with reference to Figs. 1–8.

[18484] VGAM368 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM368 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18485] VGAM368 gene encodes a VGAM368 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM368 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM368 precursor RNA is designated SEQ ID:354, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:354 is located at position 22912 relative to the genome of Avian

## Infectious Bronchitis Virus.

[18486] VGAM368 precursor RNA folds onto itself, forming VGAM368 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18487] An enzyme complex designated DICER COMPLEX, `dices` the VGAM368 folded precursor RNA into VGAM368 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 51%) nucleotide sequence of VGAM368 RNA is designated SEQ ID:3079, and is provided hereinbelow with reference to the sequence listing part.

[18488] VGAM368 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM368 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM368 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18489] VGAM368 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM368 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM368 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM368 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM368 host target RNA, herein designated VGAM HOST TARGET RNA. It is further



appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18490] The complementary binding of VGAM368 RNA, herein designated VGAM RNA, to host target binding sites on VGAM368 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM368 host target RNA into VGAM368 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18491] It is appreciated that VGAM368 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM368 host target genes. The mRNA of each one of this plurality of VGAM368 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM368 RNA, herein designated VGAM RNA, and which when bound by VGAM368 RNA causes inhibition of translation of respective one or more VGAM368 host target proteins.

[18492] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM368 gene, herein designated VGAM GENE, on one or more VGAM368 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18493] It is yet further appreciated that a function of VGAM368 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of

VGAM368 correlate with, and may be deduced from, the identity of the host target genes which VGAM368 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18494] Nucleotide sequences of the VGAM368 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM368 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM368 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM368 are further described hereinbelow with reference to Table 1.

[18495] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM368 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM368 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18496] As mentioned hereinabove with reference to Fig. 1, a function of VGAM368 gene, herein designated VGAM is inhibition of expression of VGAM368 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM368 correlate with, and may be deduced

from, the identity of the target genes which VGAM368 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18497] Aryl Hydrocarbon Receptor (AHR, Accession NM\_001621) is a VGAM368 host target gene. AHR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AHR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AHR BINDING SITE, designated SEQ ID:7337, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18498] A function of VGAM368 is therefore inhibition of Aryl Hydrocarbon Receptor (AHR, Accession NM\_001621), a gene which plays a role in modulating carcinogenesis through the induction of xenobiotic-metabolizing enzymes. Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AHR. The function of AHR has been established by previous studies. Halogenated aromatic hydrocarbons, represented by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), are envi-

ronmental pollutants that are produced by minor side-reactions in chemical manufacturing processes and by combustion of waste materials. These chemicals cause potent and pleiotropic toxicity, including teratogenesis, immune suppression, epithelial disorders, and tumor production in experimental animals. At the molecular level, aldehyde dehydrogenase, quinone reductase, and various drug-metabolizing enzymes are induced by the chemicals in some cultured cells and some tissues of experimental animals. All these biologic effects are thought to be mediated by an intracellular aryl hydrocarbon receptor (AHR). By fluorescence in situ hybridization and by DNA blot hybridization using human/mouse or human/Chinese hamster hybrid cell DNAs, Ema et al. (1994) assigned the AHR gene to 7p21. By use of PCR analysis of somatic cell hybrids and fluorescence in situ hybridization of metaphase cells, Le Beau et al. (1994) localized the AHR gene to 7p21-p15. Micka et al. (1997) localized the AHR gene to 7p15 using fluorescence in situ hybridization. Performing linkage analysis in a 3-generation family, they showed with good probability that the high CYP1A1 (OMIM Ref. No. 108330) inducibility phenotype segregates with the 7p15 region. Animal model experiments lend further sup-

port to the function of AHR. To determine whether the aryl hydrocarbon receptor plays a role in modulating carcinogenesis through the induction of xenobiotic-metabolizing enzymes, Shimizu et al. (2000) studied Ahr-deficient mice exposed to benzo(a)pyrene, a widely distributed environmental carcinogen.

[18499] It is appreciated that the abovementioned animal model for AHR is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[18500] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18501] Ema, M.; Matsushita, N.; Sogawa, K.; Ariyama, T.; Inazawa, J.; Nemoto, T.; Ota, M.; Oshimura, M.; Fujii-Kuriyama, Y. : Human arylhydrocarbon receptor: functional expression and chromosomal assignment to 7p21. J. Biochem. 116: 845-851, 1994. ; and

[18502] Shimizu, Y.; Nakatsuru, Y.; Ichinose, M.; Takahashi, Y.; Kume, H.; Mimura, J.; Fujii-Kuriyama, Y.; Ishikawa, T. : Benzo[a]pyrene carcinogenicity is lost in mice lacking the aryl hydrocar.

[18503] Further studies establishing the function and utilities of

AHR are found in John Hopkins OMIM database record ID 600253, and in cited publications numbered 8279–8281, 771 and 8282–8283 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Astrotactin (ASTN, Accession XM\_045113) is another VGAM368 host target gene. ASTN BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ASTN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASTN BINDING SITE, designated SEQ ID:34363, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18504] Another function of VGAM368 is therefore inhibition of Astrotactin (ASTN, Accession XM\_045113). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASTN. Estrogen-related Receptor Beta Like 1 (ESRRBL1, Accession NM\_018010) is another VGAM368 host target gene. ESRRBL1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ESRRBL1, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRBL1 BINDING SITE, designated SEQ ID:19740, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18505] Another function of VGAM368 is therefore inhibition of Estrogen-related Receptor Beta Like 1 (ESRRBL1, Accession NM\_018010). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESRRBL1. Guanylate Cyclase 1, Soluble, Alpha 3 (GUCY1A3, Accession XM\_032838) is another VGAM368 host target gene. GUCY1A3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GUCY1A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GUCY1A3 BINDING SITE, designated SEQ ID:31778, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18506] Another function of VGAM368 is therefore inhibition of



Guanylate Cyclase 1, Soluble, Alpha 3 (GUCY1A3, Accession XM\_032838), a gene which is alpha 1 (alpha 3) subunit of soluble guanylate cyclase and forms a heterodimer with GUCY1B3 that converts GTP to cGMP. Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GUCY1A3. The function of GUCY1A3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM206.L-3-hydroxyacyl-Coenzyme A Dehydrogenase, Short Chain (HADHSC, Accession NM\_005327) is another VGAM368 host target gene. HADHSC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HADHSC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HADHSC BINDING SITE, designated SEQ ID:11799, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18507] Another function of VGAM368 is therefore inhibition of L-3-hydroxyacyl-Coenzyme A Dehydrogenase, Short Chain

(HADHSC, Accession NM\_005327). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HADHSC. Interleukin 24 (IL24, Accession NM\_006850) is another VGAM368 host target gene. IL24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL24 BINDING SITE, designated SEQ ID:13720, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18508] Another function of VGAM368 is therefore inhibition of Interleukin 24 (IL24, Accession NM\_006850), a gene which may contribute to terminal cell differentiation. Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL24. The function of IL24 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM258. Phosphatase and Tensin Homolog (mutated in multiple advanced cancers 1) (PTEN,

Accession NM\_000314) is another VGAM368 host target gene. PTEN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTEN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTEN BINDING SITE, designated SEQ ID:5858, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18509] Another function of VGAM368 is therefore inhibition of Phosphatase and Tensin Homolog (mutated in multiple advanced cancers 1) (PTEN, Accession NM\_000314). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTEN. Retinoic Acid Receptor, Beta (RARβ, Accession NM\_016152) is another VGAM368 host target gene. RARβ BINDING SITE1 and RARβ BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RARβ, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RARβ BINDING SITE1 and RARβ BINDING SITE2, designated SEQ ID:18236 and

SEQ ID:6692 respectively, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18510] Another function of VGAM368 is therefore inhibition of Retinoic Acid Receptor, Beta (RARβ, Accession NM\_016152), a gene which is one member of the steroid/thyroid hormone receptor family of ligand-activated transcription factors. Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RARβ. The function of RARβ and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. A Kinase (PRKA) Anchor Protein 11 (AKAP11, Accession NM\_016248) is another VGAM368 host target gene. AKAP11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKAP11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP11 BINDING SITE, designated SEQ ID:18366, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ

ID:3079.

[18511] Another function of VGAM368 is therefore inhibition of A Kinase (PRKA) Anchor Protein 11 (AKAP11, Accession NM\_016248). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP11. BMF (Accession NM\_033503) is another VGAM368 host target gene. BMF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BMF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BMF BINDING SITE, designated SEQ ID:27281, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18512] Another function of VGAM368 is therefore inhibition of BMF (Accession NM\_033503). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BMF. C1q and Tumor Necrosis Factor Related Protein 7 (C1QTNF7, Accession NM\_031911) is another VGAM368 host target gene. C1QTNF7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by C1QTNF7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1QTNF7 BINDING SITE, designated SEQ ID:25667, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18513] Another function of VGAM368 is therefore inhibition of C1q and Tumor Necrosis Factor Related Protein 7 (C1QTNF7, Accession NM\_031911). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1QTNF7. Chromosome 6 Open Reading Frame 37 (C6orf37, Accession XM\_041375) is another VGAM368 host target gene. C6orf37 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C6orf37, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C6orf37 BINDING SITE, designated SEQ ID:33513, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18514] Another function of VGAM368 is therefore inhibition of Chromosome 6 Open Reading Frame 37 (C6orf37, Accession XM\_041375). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C6orf37. Claudin 1 (CLDN1, Accession NM\_021101) is another VGAM368 host target gene. CLDN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLDN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLDN1 BINDING SITE, designated SEQ ID:22082, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18515] Another function of VGAM368 is therefore inhibition of Claudin 1 (CLDN1, Accession NM\_021101). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLDN1. DKFZP434K0427 (Accession NM\_032148) is another VGAM368 host target gene. DKFZP434K0427 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DK-

FZP434K0427, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434K0427 BINDING SITE, designated SEQ ID:25840, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18516] Another function of VGAM368 is therefore inhibition of DKFZP434K0427 (Accession NM\_032148). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434K0427. DKFZP586P0123 (Accession XM\_170681) is another VGAM368 host target gene. DKFZP586P0123 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZP586P0123, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586P0123 BINDING SITE, designated SEQ ID:45465, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18517] Another function of VGAM368 is therefore inhibition of



DKFZP586P0123 (Accession XM\_170681). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586P0123. FLJ10283 (Accession NM\_018046) is another VGAM368 host target gene. FLJ10283 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10283, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10283 BINDING SITE, designated SEQ ID:19795, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18518] Another function of VGAM368 is therefore inhibition of FLJ10283 (Accession NM\_018046). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10283. FLJ10525 (Accession NM\_018126) is another VGAM368 host target gene. FLJ10525 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ10525 BINDING SITE, designated SEQ ID:19914, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18519] Another function of VGAM368 is therefore inhibition of FLJ10525 (Accession NM\_018126). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10525. KIAA0410 (Accession NM\_014778) is another VGAM368 host target gene. KIAA0410 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0410, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0410 BINDING SITE, designated SEQ ID:16615, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18520] Another function of VGAM368 is therefore inhibition of KIAA0410 (Accession NM\_014778). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0410. MGC16384 (Accession NM\_053048) is another

VGAM368 host target gene. MGC16384 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC16384, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC16384 BINDING SITE, designated SEQ ID:27595, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18521] Another function of VGAM368 is therefore inhibition of MGC16384 (Accession NM\_053048). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC16384. SAE1 (Accession NM\_005500) is another VGAM368 host target gene. SAE1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SAE1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SAE1 BINDING SITE, designated SEQ ID:12003, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18522] Another function of VGAM368 is therefore inhibition of SAE1 (Accession NM\_005500). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SAE1. SDS3 (Accession XM\_045014) is another VGAM368 host target gene. SDS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDS3 BINDING SITE, designated SEQ ID:34320, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18523] Another function of VGAM368 is therefore inhibition of SDS3 (Accession XM\_045014). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDS3. Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4G (SEMA4G, Accession XM\_170638) is another VGAM368 host target gene. SEMA4G BINDING SITE is HOST TARGET binding site found in the 5' untranslated

region of mRNA encoded by SEMA4G, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA4G BINDING SITE, designated SEQ ID:45414, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18524] Another function of VGAM368 is therefore inhibition of Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4G (SEMA4G, Accession XM\_170638). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA4G. LOC113115 (Accession NM\_138419) is another VGAM368 host target gene. LOC113115 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC113115, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC113115 BINDING SITE, designated SEQ ID:28789, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3079.

[18525] Another function of VGAM368 is therefore inhibition of LOC113115 (Accession NM\_138419). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC113115. LOC125228 (Accession XM\_058913) is another VGAM368 host target gene. LOC125228 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC125228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC125228 BINDING SITE, designated SEQ ID:36791, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18526] Another function of VGAM368 is therefore inhibition of LOC125228 (Accession XM\_058913). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125228. LOC144848 (Accession XM\_056770) is another VGAM368 host target gene. LOC144848 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144848, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144848 BINDING SITE, designated SEQ ID:36422, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18527] Another function of VGAM368 is therefore inhibition of LOC144848 (Accession XM\_056770). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144848. LOC145622 (Accession XM\_085186) is another VGAM368 host target gene. LOC145622 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145622, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145622 BINDING SITE, designated SEQ ID:37913, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18528] Another function of VGAM368 is therefore inhibition of LOC145622 (Accession XM\_085186). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC145622. LOC151996 (Accession XM\_098151) is another VGAM368 host target gene. LOC151996 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC151996, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151996 BINDING SITE, designated SEQ ID:41415, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18529] Another function of VGAM368 is therefore inhibition of LOC151996 (Accession XM\_098151). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151996. LOC157273 (Accession XM\_098743) is another VGAM368 host target gene. LOC157273 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC157273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157273 BINDING SITE, designated SEQ ID:41780, to



the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18530] Another function of VGAM368 is therefore inhibition of LOC157273 (Accession XM\_098743). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157273. LOC160897 (Accession XM\_090573) is another VGAM368 host target gene. LOC160897 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC160897, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC160897 BINDING SITE, designated SEQ ID:40010, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18531] Another function of VGAM368 is therefore inhibition of LOC160897 (Accession XM\_090573). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC160897. LOC200347 (Accession XM\_114219) is another VGAM368 host target gene. LOC200347 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC200347, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200347 BINDING SITE, designated SEQ ID:42807, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18532] Another function of VGAM368 is therefore inhibition of LOC200347 (Accession XM\_114219). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200347. LOC220729 (Accession XM\_049575) is another VGAM368 host target gene. LOC220729 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220729, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220729 BINDING SITE, designated SEQ ID:35448, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18533] Another function of VGAM368 is therefore inhibition of LOC220729 (Accession XM\_049575). Accordingly, utilities

of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220729. LOC256337 (Accession XM\_170643) is another VGAM368 host target gene. LOC256337 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC256337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256337 BINDING SITE, designated SEQ ID:45419, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18534] Another function of VGAM368 is therefore inhibition of LOC256337 (Accession XM\_170643). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256337. LOC90342 (Accession XM\_031009) is another VGAM368 host target gene. LOC90342 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90342, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC90342 BINDING SITE, designated SEQ ID:31256, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18535] Another function of VGAM368 is therefore inhibition of LOC90342 (Accession XM\_031009). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90342. LOC96810 (Accession XM\_047273) is another VGAM368 host target gene. LOC96810 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC96810, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC96810 BINDING SITE, designated SEQ ID:34926, to the nucleotide sequence of VGAM368 RNA, herein designated VGAM RNA, also designated SEQ ID:3079.

[18536] Another function of VGAM368 is therefore inhibition of LOC96810 (Accession XM\_047273). Accordingly, utilities of VGAM368 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC96810. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 369 (VGAM369) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18537] VGAM369 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM369 was detected is described hereinabove with reference to Figs. 1–8.

[18538] VGAM369 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM369 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18539] VGAM369 gene encodes a VGAM369 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM369 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM369 precursor RNA is designated SEQ ID:355, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:355 is located at position 16684 relative to the genome of Avian

## Infectious Bronchitis Virus.

[18540] VGAM369 precursor RNA folds onto itself, forming VGAM369 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18541] An enzyme complex designated DICER COMPLEX, `dices` the VGAM369 folded precursor RNA into VGAM369 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM369 RNA is designated SEQ ID:3080, and is provided hereinbelow with reference to the sequence listing part.

[18542] VGAM369 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM369 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM369 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18543] VGAM369 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM369 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM369 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM369 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM369 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[18544] The complementary binding of VGAM369 RNA, herein designated VGAM RNA, to host target binding sites on VGAM369 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM369 host target RNA into VGAM369 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18545] It is appreciated that VGAM369 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM369 host target genes. The mRNA of each one of this plurality of VGAM369 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM369 RNA, herein designated VGAM RNA, and which when bound by VGAM369 RNA causes inhibition of translation of respective one or more VGAM369 host target proteins.



[18546] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM369 gene, herein designated VGAM GENE, on one or more VGAM369 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18547] It is yet further appreciated that a function of VGAM369 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of

VGAM369 correlate with, and may be deduced from, the identity of the host target genes which VGAM369 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18548] Nucleotide sequences of the VGAM369 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM369 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM369 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM369 are further described hereinbelow with reference to Table 1.

[18549] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM369 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM369 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18550] As mentioned hereinabove with reference to Fig. 1, a function of VGAM369 gene, herein designated VGAM is inhibition of expression of VGAM369 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM369 correlate with, and may be deduced

from, the identity of the target genes which VGAM369 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18551] Cullin 3 (CUL3, Accession NM\_003590) is a VGAM369 host target gene. CUL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CUL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CUL3 BINDING SITE, designated SEQ ID:9645, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18552] A function of VGAM369 is therefore inhibition of Cullin 3 (CUL3, Accession NM\_003590), a gene which may target other proteins for ubiquitin-dependent proteolysis. Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CUL3. The function of CUL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM143.Dihydropyrimidinase-like 3 (DPYSL3, Accession

NM\_001387) is another VGAM369 host target gene. DPYSL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DPYSL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DPYSL3 BINDING SITE, designated SEQ ID:7071, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18553] Another function of VGAM369 is therefore inhibition of Dihydropyrimidinase-like 3 (DPYSL3, Accession NM\_001387), a gene which is a member of the dihydropyrimidinase family. Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DPYSL3. The function of DPYSL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM24. Nuclear Factor (erythroid-derived 2)-like 1 (NFE2L1, Accession NM\_003204) is another VGAM369 host target gene. NFE2L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by NFE2L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFE2L1 BINDING SITE, designated SEQ ID:9196, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18554] Another function of VGAM369 is therefore inhibition of Nuclear Factor (erythroid-derived 2)-like 1 (NFE2L1, Accession NM\_003204), a gene which may regulate expression of ferritin genes. Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NFE2L1. The function of NFE2L1 has been established by previous studies. Chan et al. (1993) devised a complementation assay in yeast to clone mammalian transcription activators and used it to identify a distinct human bZIP transcription factor, NFE2L1, which they designated NRF1 (NFE2-related factor-1) because of its similarities to NFE2 (OMIM Ref. No. 601490). Chan et al. (1995) showed that the NFE2L1 gene encodes a 742-amino acid protein with a different molecular weight than either the p45 subunit (NFE2) or the Maf protein subunit (MafF, MafG (OMIM Ref. No.

602020), or MafK (OMIM Ref. No. 600197)) of nuclear factor erythroid-2. Chan et al. (1993) found that NFE2L1 activates transcription via NFE2-binding sites in yeast cells. The ubiquitous expression pattern of NFE2L1 and the range of promoters containing the NFE2-binding motif suggested that this gene may play a role in the regulation of heme synthesis and ferritin genes. Animal model experiments lend further support to the function of NFE2L1. To determine the function of Nrf1, Chan et al. (1998) disrupted the mouse gene by homologous recombination. Heterozygous Nrf1 mutant mice developed normally, were fertile, and showed no obvious abnormalities. Mice homozygous for the Nrf1 mutation suffered from anemia as a result of abnormal fetal liver erythropoiesis and died in utero at mid-late gestation. The authors did not detect defects in globin gene expression. Abnormal red cell production appeared to result from a defect in the fetal liver microenvironment specific for erythroid cells. Chan et al. (1998) suggested that target genes regulated by Nrf1 play an essential role during fetal liver hematopoiesis.

[18555] It is appreciated that the abovementioned animal model for NFE2L1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further ap-

preciated from the publications sited hereinbelow.

[18556] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18557] Chan, J. Y.; Kwong, M.; Lu, R.; Chang, J.; Wang, B.; Yen, T. S. B.; Kan, Y. W. : Targeted disruption of the ubiquitous CNC-bZIP transcription factor, Nrf-1, results in anemia and embryonic lethality in mice. EMBO J. 17: 1779-1787, 1998. ; and

[18558] Chan, J. Y.; Han, X.-L.; Kan, Y. W. : Cloning of Nrf1, an NF-E2-related transcription factor, by genetic selection in yeast. Proc. Nat. Acad. Sci. 90: 11371-11375, 1993.

[18559] Further studies establishing the function and utilities of NFE2L1 are found in John Hopkins OMIM database record ID 163260, and in sited publications numbered 10585-10591 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Single-minded Homolog 2 (Drosophila) (SIM2, Accession NM\_005069) is another VGAM369 host target gene. SIM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-

ble 2 illustrates the complementarity of the nucleotide sequences of SIM2 BINDING SITE, designated SEQ ID:11517, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18560] Another function of VGAM369 is therefore inhibition of Single-minded Homolog 2 (Drosophila) (SIM2, Accession NM\_005069), a gene which may be a master gene of cns development. Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIM2. The function of SIM2 has been established by previous studies. Dahmane et al. (1995) noted that many features of Down syndrome might result from the overdosage of only a few genes located in the DCR around the 21q22.2 subband. To search for these genes, cosmids mapping to this region were isolated by Dahmane et al. (1995) and used for trapping exons. One of the trapped exons obtained had a sequence very similar to part of the Drosophila sim gene. Mapping data indicated that this exonic sequence is present only in the DCR in the human genome. Hybridization of this exonic sequence with human fetal kidney polyadenylated RNA revealed 2 transcripts of 6 and 4.3 kb. In situ hybridization of a probe derived from this exon with human and rat fe-



tuses showed that the corresponding gene is expressed during early fetal life in the central nervous system and in other tissues, including the facial, skeletal, palate, and vertebra primordia. The expression pattern of this gene suggested to the authors that it may be involved in the pathogenesis of some of the morphologic features and brain anomalies of Down syndrome. Animal model experiments lend further support to the function of SIM2. Chrast et al. (2000) created a bacterial artificial chromosome transgenic mice with 1 or 2 additional copies of mouse Sim2. The transgene was expressed in the same spatial pattern as the endogenous gene. The mice developed normally, were fertile, and did not show detectable histopathologic abnormalities. However, detailed analysis of their behavior revealed anxiety-related/reduced exploratory behavior and sensitivity to pain, phenotypes similar to those also present in other partial trisomy 16 mouse models of DS. The authors suggested that overexpression of SIM2 may contribute to the DS behavioral phenotype.

[18561] It is appreciated that the abovementioned animal model for SIM2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appre-

ciated from the publications sited hereinbelow.

[18562] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18563] Dahmane, N.; Charron, G.; Lopes, C.; Yaspo, M.-L.; Maunoury, C.; Decorte, L.; Sinet, P.-M.; Bloch, B.; Delabar, J.-M. : Down syndrome-critical region contains a gene homologous to *Drosophila* sim expressed during rat and human central nervous system development. *Proc. Nat. Acad. Sci.* 92: 9191-9195, 1995. ; and

[18564] Chrast, R.; Scott, H. S.; Madani, R.; Huber, L.; Wolfer, D. P.; Prinz, M.; Aguzzi, A.; Lipp, H.-P.; Antonarakis, S. E. : Mice trisomic for a bacterial artificial chromosome with the sim.

[18565] Further studies establishing the function and utilities of SIM2 are found in John Hopkins OMIM database record ID 600892, and in sited publications numbered 9290-929 and 9296 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SORCS1 (Accession NM\_052918) is another VGAM369 host target gene. SORCS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SORCS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of SORCS1 BINDING SITE, designated SEQ ID:27483, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18566] Another function of VGAM369 is therefore inhibition of SORCS1 (Accession NM\_052918). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORCS1. TNF Receptor-associated Factor 1 (TRAF1, Accession NM\_005658) is another VGAM369 host target gene. TRAF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRAF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRAF1 BINDING SITE, designated SEQ ID:12198, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18567] Another function of VGAM369 is therefore inhibition of TNF Receptor-associated Factor 1 (TRAF1, Accession NM\_005658), a gene which signal transducer associated

with the cytoplasmic domain of the 75 kda tumor necrosis factor receptor (tnf-r2). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRAF1. The function of TRAF1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM250. Vinculin (VCL, Accession NM\_003373) is another VGAM369 host target gene. VCL BINDING SITE1 and VCL BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by VCL, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VCL BINDING SITE1 and VCL BINDING SITE2, designated SEQ ID:9402 and SEQ ID:15191 respectively, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18568] Another function of VGAM369 is therefore inhibition of Vinculin (VCL, Accession NM\_003373). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VCL. FLJ20273 (Accession NM\_019027) is another

VGAM369 host target gene. FLJ20273 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20273 BINDING SITE, designated SEQ ID:21115, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18569] Another function of VGAM369 is therefore inhibition of FLJ20273 (Accession NM\_019027). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20273. FLJ21865 (Accession NM\_022759) is another VGAM369 host target gene. FLJ21865 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21865, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21865 BINDING SITE, designated SEQ ID:23001, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18570] Another function of VGAM369 is therefore inhibition of FLJ21865 (Accession NM\_022759). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21865. G Protein-coupled Receptor Kinase-interactor 1 (GIT1, Accession NM\_014030) is another VGAM369 host target gene. GIT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GIT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GIT1 BINDING SITE, designated SEQ ID:15258, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18571] Another function of VGAM369 is therefore inhibition of G Protein-coupled Receptor Kinase-interactor 1 (GIT1, Accession NM\_014030). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GIT1. KIAA0210 (Accession NM\_014744) is another VGAM369 host target gene. KIAA0210 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0210, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0210 BINDING SITE, designated SEQ ID:16421, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18572] Another function of VGAM369 is therefore inhibition of KIAA0210 (Accession NM\_014744). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0210. KIAA0336 (Accession NM\_014635) is another VGAM369 host target gene. KIAA0336 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0336, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0336 BINDING SITE, designated SEQ ID:16011, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18573] Another function of VGAM369 is therefore inhibition of KIAA0336 (Accession NM\_014635). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0336. KIAA1130 (Accession XM\_031104) is another VGAM369 host target gene. KIAA1130 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1130, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1130 BINDING SITE, designated SEQ ID:31287, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18574] Another function of VGAM369 is therefore inhibition of KIAA1130 (Accession XM\_031104). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1130. KIAA1831 (Accession XM\_033366) is another VGAM369 host target gene. KIAA1831 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1831, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1831 BINDING SITE, designated SEQ ID:31907, to the



nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18575] Another function of VGAM369 is therefore inhibition of KIAA1831 (Accession XM\_033366). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1831. MCJ (Accession NM\_013238) is another VGAM369 host target gene. MCJ BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MCJ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MCJ BINDING SITE, designated SEQ ID:14899, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18576] Another function of VGAM369 is therefore inhibition of MCJ (Accession NM\_013238). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MCJ. Rabip4R (Accession NM\_017987) is another VGAM369 host target gene. Rabip4R BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA en-

coded by Rabip4R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Rabip4R BINDING SITE, designated SEQ ID:19717, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18577] Another function of VGAM369 is therefore inhibition of Rabip4R (Accession NM\_017987). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rabip4R. Spi-B Transcription Factor (Spi-1/PU.1 related) (SPIB, Accession NM\_003121) is another VGAM369 host target gene. SPIB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPIB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPIB BINDING SITE, designated SEQ ID:9093, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18578] Another function of VGAM369 is therefore inhibition of Spi-B Transcription Factor (Spi-1/PU.1 related) (SPIB, Ac-

cession NM\_003121). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPIB. Ubinuclein 1 (UBN1, Accession NM\_016936) is another VGAM369 host target gene. UBN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBN1 BINDING SITE, designated SEQ ID:18854, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18579] Another function of VGAM369 is therefore inhibition of Ubinuclein 1 (UBN1, Accession NM\_016936). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBN1. LOC145368 (Accession XM\_085112) is another VGAM369 host target gene. LOC145368 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145368, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of LOC145368 BINDING SITE, designated SEQ ID:37830, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18580] Another function of VGAM369 is therefore inhibition of LOC145368 (Accession XM\_085112). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145368. LOC150423 (Accession XM\_086912) is another VGAM369 host target gene. LOC150423 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150423 BINDING SITE, designated SEQ ID:38970, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18581] Another function of VGAM369 is therefore inhibition of LOC150423 (Accession XM\_086912). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150423. LOC153232 (Accession XM\_098331) is an-

other VGAM369 host target gene. LOC153232 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC153232, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153232 BINDING SITE, designated SEQ ID:41597, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18582] Another function of VGAM369 is therefore inhibition of LOC153232 (Accession XM\_098331). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153232. LOC221486 (Accession XM\_165760) is another VGAM369 host target gene. LOC221486 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221486, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221486 BINDING SITE, designated SEQ ID:43746, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18583] Another function of VGAM369 is therefore inhibition of LOC221486 (Accession XM\_165760). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221486. LOC256310 (Accession XM\_172813) is another VGAM369 host target gene. LOC256310 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256310, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256310 BINDING SITE, designated SEQ ID:46096, to the nucleotide sequence of VGAM369 RNA, herein designated VGAM RNA, also designated SEQ ID:3080.

[18584] Another function of VGAM369 is therefore inhibition of LOC256310 (Accession XM\_172813). Accordingly, utilities of VGAM369 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256310. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 370 (VGAM370) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[18585] VGAM370 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM370 was detected is described hereinabove with reference to Figs. 1–8.

[18586] VGAM370 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM370 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18587] VGAM370 gene encodes a VGAM370 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM370 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM370 precursor RNA is designated SEQ ID:356, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:356 is located at position 17287 relative to the genome of Avian Infectious Bronchitis Virus.

[18588] VGAM370 precursor RNA folds onto itself, forming VGAM370 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[18589] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM370 folded precursor RNA into VGAM370 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 42%) nucleotide se-  
quence of VGAM370 RNA is designated SEQ ID:3081, and  
is provided hereinbelow with reference to the sequence  
listing part.

[18590] VGAM370 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM370 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM370 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding



gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18591] VGAM370 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM370 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM370 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM370 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM370 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18592] The complementary binding of VGAM370 RNA, herein designated VGAM RNA, to host target binding sites on VGAM370 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM370 host target RNA into VGAM370 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18593] It is appreciated that VGAM370 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM370 host target genes. The mRNA of each one of this plurality of VGAM370 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM370 RNA, herein designated VGAM RNA, and which when bound by VGAM370 RNA causes inhibition of translation of respective one or more VGAM370 host target proteins.

[18594] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM370 gene, herein designated VGAM GENE, on one or more VGAM370 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18595] It is yet further appreciated that a function of VGAM370 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM370 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM370 correlate with, and may be deduced from, the identity of the host target genes which VGAM370 binds and inhibits, and the function of these host target genes,

as elaborated hereinbelow.

[18596] Nucleotide sequences of the VGAM370 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM370 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM370 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM370 are further described hereinbelow with reference to Table 1.

[18597] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM370 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM370 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18598] As mentioned hereinabove with reference to Fig. 1, a function of VGAM370 gene, herein designated VGAM is inhibition of expression of VGAM370 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM370 correlate with, and may be deduced from, the identity of the target genes which VGAM370 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18599] N-ethylmaleimide-sensitive Factor (NSF, Accession XM\_032173) is a VGAM370 host target gene. NSF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NSF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NSF BINDING SITE, designated SEQ ID:31586, to the nucleotide sequence of VGAM370 RNA, herein designated VGAM RNA, also designated SEQ ID:3081.

[18600] A function of VGAM370 is therefore inhibition of N-ethylmaleimide-sensitive Factor (NSF, Accession XM\_032173), a gene which catalyzes the fusion of transport vesicles within the golgi cisternae. Accordingly, utilities of VGAM370 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NSF. The function of NSF has been established by previous studies. The process of vesicle targeting and fusion in the secretory and endocytic pathways has been described by the SNAREs hypothesis (Rothman, 1994). This proposes that vesicles dock with specific target membranes by binding to membrane-specific SNAREs (soluble N-ethylmaleimide-sensitive factors attachment protein re-

ceptors). Hoyle et al. (1996) noted that targeting specificity is also affected by the Rabs, a group of small soluble GTPases. After the vesicle has bound to the target membrane, the SNARE multimer is joined by the soluble SNAP proteins and N-ethylmaleimide-sensitive factor (NSF). The resulting large complex is thought to allow membrane fusion and the ATPase activity of the NSF appears to be essential for the process. Hoyle et al. (1996) stated that while many of different SNAREs, Rabs, and SNAPs are involved in membrane fusion, there is only 1 NSF, and the SNARE hypothesis describes NSF-dependent fusion. Mammalian N-ethylmaleimide-sensitive protein was first described by Glick and Rothman (1987) as the protein that restored the ability of Golgi membranes that had been inactivated with the reagent N-ethylmaleimide to re-engage in vesicular transport. The NSF gene was subsequently cloned from Chinese hamster cells by Block et al. (1988) and Wilson et al. (1989). NSF is a member of the AAA (ATPases associated with diverse cellular activities) gene family. Hoyle et al. (1996) stated that the genes are most related throughout the approximately 200-amino acid domain (the AAA domain) that binds ATP; however, the family is notable not only for its conservation but also for

diverse functions of its proteins in eukaryotic cells. The family can be subdivided into those with either 1 or 2 ATP-binding domains. NSF is a 2-domain member of the AAA family. Valosin-containing protein (OMIM Ref. No. 601023), which is also involved in membrane fusion, is another 2-AAA domain protein.

[18601] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18602] Glick, B. S.; Rothman, J. E. : Possible role for fatty acyl-coenzyme A in intracellular protein transport. *Nature* 326: 309-312, 1987. ; and

[18603] Hoyle, J.; Phelan, J. P.; Bermingham, N.; Fisher, E. M. C. : Localization of human and mouse N-ethylmaleimide-sensitive factor (NSF) gene: a two-domain member of the AAA family that is i.

[18604] Further studies establishing the function and utilities of NSF are found in John Hopkins OMIM database record ID 601633, and in cited publications numbered 2808-281 and 12358-2812 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Mitochondrial Ribosomal Protein L20 (MRPL20, Accession NM\_017971) is another VGAM370 host target

gene. MRPL20 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MRPL20, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MRPL20 BINDING SITE, designated SEQ ID:19699, to the nucleotide sequence of VGAM370 RNA, herein designated VGAM RNA, also designated SEQ ID:3081.

[18605] Another function of VGAM370 is therefore inhibition of Mitochondrial Ribosomal Protein L20 (MRPL20, Accession NM\_017971). Accordingly, utilities of VGAM370 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MRPL20. NUCKS (Accession NM\_022731) is another VGAM370 host target gene. NUCKS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUCKS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUCKS BINDING SITE, designated SEQ ID:22936, to the nucleotide sequence of VGAM370 RNA, herein designated VGAM RNA, also designated SEQ



ID:3081.

[18606] Another function of VGAM370 is therefore inhibition of NUCKS (Accession NM\_022731). Accordingly, utilities of VGAM370 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUCKS. LOC146138 (Accession XM\_096938) is another VGAM370 host target gene. LOC146138 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146138, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146138 BINDING SITE, designated SEQ ID:40659, to the nucleotide sequence of VGAM370 RNA, herein designated VGAM RNA, also designated SEQ ID:3081.

[18607] Another function of VGAM370 is therefore inhibition of LOC146138 (Accession XM\_096938). Accordingly, utilities of VGAM370 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146138. LOC254250 (Accession XM\_173093) is another VGAM370 host target gene. LOC254250 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254250, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254250 BINDING SITE, designated SEQ ID:46356, to the nucleotide sequence of VGAM370 RNA, herein designated VGAM RNA, also designated SEQ ID:3081.

[18608] Another function of VGAM370 is therefore inhibition of LOC254250 (Accession XM\_173093). Accordingly, utilities of VGAM370 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254250. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 371 (VGAM371) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18609] VGAM371 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM371 was detected is described hereinabove with reference to Figs. 1–8.

[18610] VGAM371 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bron-

chitis Virus. VGAM371 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18611] VGAM371 gene encodes a VGAM371 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM371 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM371 precursor RNA is designated SEQ ID:357, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:357 is located at position 16829 relative to the genome of Avian Infectious Bronchitis Virus.

[18612] VGAM371 precursor RNA folds onto itself, forming VGAM371 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18613] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM371 folded precursor RNA into VGAM371 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM371 RNA is designated SEQ ID:3082, and is provided hereinbelow with reference to the sequence listing part.

[18614] VGAM371 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM371 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM371 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18615] VGAM371 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM371 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM371 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM371 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM371 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18616] The complementary binding of VGAM371 RNA, herein designated VGAM RNA, to host target binding sites on VGAM371 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM371 host target RNA into VGAM371 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18617] It is appreciated that VGAM371 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM371 host target genes. The mRNA of each one of this plurality of VGAM371 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM371 RNA, herein designated VGAM RNA, and which when bound by VGAM371 RNA causes inhibition of translation of respective one or more VGAM371 host target proteins.

[18618] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM371 gene, herein designated VGAM GENE, on one or more VGAM371 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18619] It is yet further appreciated that a function of VGAM371 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM371 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM371 correlate with, and may be deduced from, the identity of the host target genes which VGAM371 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18620] Nucleotide sequences of the VGAM371 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM371 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM371 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM371 are further described hereinbelow with reference to Table 1.

[18621] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM371 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM371 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18622] As mentioned hereinabove with reference to Fig. 1, a function of VGAM371 gene, herein designated VGAM is inhibition of expression of VGAM371 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM371 correlate with, and may be deduced from, the identity of the target genes which VGAM371 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18623] SRGAP2 (Accession XM\_059095) is a VGAM371 host target gene. SRGAP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SRGAP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRGAP2 BINDING SITE, designated SEQ ID:36877, to the nucleotide sequence of VGAM371 RNA,



herein designated VGAM RNA, also designated SEQ ID:3082.

[18624] A function of VGAM371 is therefore inhibition of SRGAP2 (Accession XM\_059095). Accordingly, utilities of VGAM371 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRGAP2. ADAMTS-like 1 (ADAMTSL1, Accession NM\_139264) is another VGAM371 host target gene. ADAMTSL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAMTSL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAMTSL1 BINDING SITE, designated SEQ ID:29253, to the nucleotide sequence of VGAM371 RNA, herein designated VGAM RNA, also designated SEQ ID:3082.

[18625] Another function of VGAM371 is therefore inhibition of ADAMTS-like 1 (ADAMTSL1, Accession NM\_139264). Accordingly, utilities of VGAM371 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAMTSL1. Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3, Accession NM\_004273) is another VGAM371 host target gene. CHST3 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHST3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST3 BINDING SITE, designated SEQ ID:10472, to the nucleotide sequence of VGAM371 RNA, herein designated VGAM RNA, also designated SEQ ID:3082.

[18626] Another function of VGAM371 is therefore inhibition of Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3, Accession NM\_004273). Accordingly, utilities of VGAM371 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHST3. KIAA1344 (Accession XM\_051699) is another VGAM371 host target gene. KIAA1344 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1344, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1344 BINDING SITE, designated SEQ ID:35868, to the nucleotide sequence of VGAM371 RNA, herein designated VGAM RNA, also designated SEQ ID:3082.

[18627] Another function of VGAM371 is therefore inhibition of KIAA1344 (Accession XM\_051699). Accordingly, utilities of VGAM371 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1344. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 372 (VGAM372) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18628] VGAM372 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM372 was detected is described hereinabove with reference to Figs. 1–8.

[18629] VGAM372 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM372 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18630] VGAM372 gene encodes a VGAM372 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM372

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM372 precursor RNA is designated SEQ ID:358, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:358 is located at position 11416 relative to the genome of Avian Infectious Bronchitis Virus.

[18631] VGAM372 precursor RNA folds onto itself, forming VGAM372 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18632] An enzyme complex designated DICER COMPLEX, `dices` the VGAM372 folded precursor RNA into VGAM372 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 53%) nucleotide sequence of VGAM372 RNA is designated SEQ ID:3083, and is provided hereinbelow with reference to the sequence listing part.

[18633] VGAM372 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM372 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM372 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[18634] VGAM372 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM372 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM372 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM372 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM372 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18635] The complementary binding of VGAM372 RNA, herein designated VGAM RNA, to host target binding sites on VGAM372 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM372 host target RNA into VGAM372 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18636] It is appreciated that VGAM372 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM372 host target genes. The mRNA of each one of this plurality of VGAM372 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM372 RNA, herein designated VGAM RNA, and which when bound by VGAM372 RNA causes inhibition of translation of respective one or more VGAM372 host target proteins.

[18637] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM372 gene, herein designated VGAM GENE, on one or more VGAM372 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18638] It is yet further appreciated that a function of VGAM372 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM372 correlate with, and may be deduced from, the identity of the host target genes which VGAM372 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18639] Nucleotide sequences of the VGAM372 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM372 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM372 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM372 are further described hereinbelow with reference to Table 1.

[18640] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM372 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM372 RNA, herein designated VGAM RNA, are described hereinbelow with refer-



ence to Table 2.

[18641] As mentioned hereinabove with reference to Fig. 1, a function of VGAM372 gene, herein designated VGAM is inhibition of expression of VGAM372 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM372 correlate with, and may be deduced from, the identity of the target genes which VGAM372 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18642] Annexin A8 (ANXA8, Accession NM\_001630) is a VGAM372 host target gene. ANXA8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ANXA8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANXA8 BINDING SITE, designated SEQ ID:7339, to the nucleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18643] A function of VGAM372 is therefore inhibition of Annexin A8 (ANXA8, Accession NM\_001630), a gene which acts as an indirect inhibitor of the thromboplastin-specific complex, which is involved in the blood coagulation cascade.

Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANXA8. The function of ANXA8 has been established by previous studies. Human annexin VIII was originally identified by Hauptmann et al. (1989) from a 2-kb cDNA transcript containing an open reading frame that encoded a 327-amino acid protein termed vascular anticoagulant beta. It is a minor annexin (see OMIM Ref. No. ANXA2; 151740) in human placenta and shows restricted expression in lung endothelia, skin, liver, and kidney. The gene is selectively overexpressed in acute myelocytic leukemia (Chang et al., 1992). Affected human promyelocytes contain a nonrandom chromosomal translocation breakpoint involving chromosomes 15 and 17 and creating 2 hybrid mRNA fusion products and chimeric proteins. These involve the retinoic acid receptor alpha locus (RARA; 180240) on 17q12 and the promyelocytic leukemia locus (PML; 102578) on 15q22. Chambers et al. (1992) mapped the ANXA8 gene to 10q11.2 by fluorescence in situ hybridization, thus excluding its direct involvement in the breakpoint region. However, strong overexpression of annexin VIII in this disorder could be repressed by retinoic acid-induced expression of the

## RARA gene product

- [18644] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [18645] Chang, K.-S.; Wang, G.; Freireich, E. J.; Daly, M.; Naylor, S. L.; Trujillo, J. M.; Stass, S. A. : Specific expression of the annexin VIII gene in acute promyelocytic leukemia. *Blood* 79: 1802–1810, 1992. ; and
- [18646] Sarkar, A.; Yang, P.; Fan, Y.-H.; Mu, Z. M.; Hauptmann, R.; Adolf, G. R.; Stass, S. A.; Chang, K.-S. : Regulation of the expression of annexin VIII in acute promyelocytic leukemia. *Blood*.
- [18647] Further studies establishing the function and utilities of ANXA8 are found in John Hopkins OMIM database record ID 602396, and in cited publications numbered 5902–5904, 484 and 5905 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Inositol Polyphosphate-5-phosphatase, 75kDa (INPP5B, Accession XM\_170949) is another VGAM372 host target gene. INPP5B BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by INPP5B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BIND-

ING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of INPP5B BINDING SITE, designated SEQ ID:45734, to the nucleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18648] Another function of VGAM372 is therefore inhibition of Inositol Polyphosphate-5-phosphatase, 75kDa (INPP5B, Accession XM\_170949), a gene which hydrolyzes the calcium-mobilizing second messenger  $\text{ins}(1,4,5)\text{p3}$ . Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with INPP5B. The function of INPP5B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM50.N-ethylmaleimide-sensitive Factor (NSF, Accession XM\_032173) is another VGAM372 host target gene. NSF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NSF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NSF BINDING SITE, designated SEQ ID:31588, to the nu-

cleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18649] Another function of VGAM372 is therefore inhibition of N-ethylmaleimide-sensitive Factor (NSF, Accession XM\_032173), a gene which catalyzes the fusion of transport vesicles within the golgi cisternae. Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NSF. The function of NSF and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM370. Chromosome 13 Open Reading Frame 1 (C13orf1, Accession NM\_020456) is another VGAM372 host target gene. C13orf1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C13orf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C13orf1 BINDING SITE, designated SEQ ID:21690, to the nucleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18650] Another function of VGAM372 is therefore inhibition of

Chromosome 13 Open Reading Frame 1 (C13orf1, Accession NM\_020456). Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C13orf1. MGC12972 (Accession NM\_032683) is another VGAM372 host target gene. MGC12972 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC12972, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC12972 BINDING SITE, designated SEQ ID:26405, to the nucleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18651] Another function of VGAM372 is therefore inhibition of MGC12972 (Accession NM\_032683). Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC12972. Paternally Expressed 10 (PEG10, Accession NM\_015068) is another VGAM372 host target gene. PEG10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PEG10, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PEG10 BINDING SITE, designated SEQ ID:17429, to the nucleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18652] Another function of VGAM372 is therefore inhibition of Paternally Expressed 10 (PEG10, Accession NM\_015068). Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PEG10. LOC142972 (Accession XM\_036593) is another VGAM372 host target gene. LOC142972 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC142972, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC142972 BINDING SITE, designated SEQ ID:32476, to the nucleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18653] Another function of VGAM372 is therefore inhibition of LOC142972 (Accession XM\_036593). Accordingly, utilities

of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC142972. LOC92140 (Accession XM\_043070) is another VGAM372 host target gene. LOC92140 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92140, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92140 BINDING SITE, designated SEQ ID:33889, to the nucleotide sequence of VGAM372 RNA, herein designated VGAM RNA, also designated SEQ ID:3083.

[18654] Another function of VGAM372 is therefore inhibition of LOC92140 (Accession XM\_043070). Accordingly, utilities of VGAM372 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92140. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 373 (VGAM373) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.



[18655] VGAM373 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM373 was detected is described hereinabove with reference to Figs. 1–8.

[18656] VGAM373 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM373 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18657] VGAM373 gene encodes a VGAM373 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM373 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM373 precursor RNA is designated SEQ ID:359, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:359 is located at position 14350 relative to the genome of Avian Infectious Bronchitis Virus.

[18658] VGAM373 precursor RNA folds onto itself, forming VGAM373 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18659] An enzyme complex designated DICER COMPLEX, `dices` the VGAM373 folded precursor RNA into VGAM373 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 49%) nucleotide sequence of VGAM373 RNA is designated SEQ ID:3084, and is provided hereinbelow with reference to the sequence listing part.

[18660] VGAM373 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM373 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM373 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[18661] VGAM373 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM373 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM373 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM373 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM373 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18662] The complementary binding of VGAM373 RNA, herein designated VGAM RNA, to host target binding sites on VGAM373 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM373 host target RNA into VGAM373 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18663] It is appreciated that VGAM373 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM373 host target genes. The mRNA of each one of this plurality of VGAM373 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM373 RNA, herein designated VGAM RNA, and which when bound by VGAM373 RNA causes inhibition of translation of respective one or more VGAM373 host target proteins.

[18664] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM373 gene, herein designated VGAM GENE, on one or more VGAM373 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18665] It is yet further appreciated that a function of VGAM373 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM373 correlate with, and may be deduced from, the identity of the host target genes which VGAM373 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18666] Nucleotide sequences of the VGAM373 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM373 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM373 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM373 are further  
described hereinbelow with reference to Table 1.

[18667] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM373 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM373 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[18668] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM373 gene, herein designated VGAM is  
inhibition of expression of VGAM373 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM373 correlate with, and may be deduced  
from, the identity of the target genes which VGAM373  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[18669] Potassium Inwardly-rectifying Channel, Subfamily J, Mem-  
ber 15 (KCNJ15, Accession NM\_002243) is a VGAM373

host target gene. KCNJ15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNJ15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNJ15 BINDING SITE, designated SEQ ID:8031, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18670] A function of VGAM373 is therefore inhibition of Potassium Inwardly-rectifying Channel, Subfamily J, Member 15 (KCNJ15, Accession NM\_002243). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNJ15. Cyclin M1 (CNNM1, Accession NM\_020348) is another VGAM373 host target gene. CNNM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNNM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNNM1 BINDING SITE, designated SEQ ID:21605, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA,

also designated SEQ ID:3084.

[18671] Another function of VGAM373 is therefore inhibition of Cyclin M1 (CNNM1, Accession NM\_020348). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNNM1. DKFZp761N1114 (Accession XM\_086327) is another VGAM373 host target gene. DKFZp761N1114 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp761N1114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761N1114 BINDING SITE, designated SEQ ID:38606, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18672] Another function of VGAM373 is therefore inhibition of DKFZp761N1114 (Accession XM\_086327). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761N1114. KIAA0323 (Accession XM\_032634) is another VGAM373 host target gene. KIAA0323 BINDING SITE is HOST TARGET binding site found in the 3` un-



translated region of mRNA encoded by KIAA0323, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0323 BINDING SITE, designated SEQ ID:31688, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18673] Another function of VGAM373 is therefore inhibition of KIAA0323 (Accession XM\_032634). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0323. KIAA0848 (Accession NM\_014926) is another VGAM373 host target gene. KIAA0848 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0848 BINDING SITE, designated SEQ ID:17213, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18674] Another function of VGAM373 is therefore inhibition of KIAA0848 (Accession NM\_014926). Accordingly, utilities

of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0848. KIAA1200 (Accession XM\_031054) is another VGAM373 host target gene. KIAA1200 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1200, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1200 BINDING SITE, designated SEQ ID:31262, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18675] Another function of VGAM373 is therefore inhibition of KIAA1200 (Accession XM\_031054). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1200. Mitogen-activated Protein Kinase 11 (MAPK11, Accession NM\_002751) is another VGAM373 host target gene. MAPK11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAPK11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of MAPK11 BINDING SITE, designated SEQ ID:8627, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18676] Another function of VGAM373 is therefore inhibition of Mitogen-activated Protein Kinase 11 (MAPK11, Accession NM\_002751). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPK11. LOC133418 (Accession XM\_059649) is another VGAM373 host target gene. LOC133418 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133418, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133418 BINDING SITE, designated SEQ ID:37041, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18677] Another function of VGAM373 is therefore inhibition of LOC133418 (Accession XM\_059649). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC133418. LOC153338 (Accession XM\_098361) is another VGAM373 host target gene. LOC153338 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC153338, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153338 BINDING SITE, designated SEQ ID:41609, to the nucleotide sequence of VGAM373 RNA, herein designated VGAM RNA, also designated SEQ ID:3084.

[18678] Another function of VGAM373 is therefore inhibition of LOC153338 (Accession XM\_098361). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153338. LOC255098 (Accession XM\_170912) is another VGAM373 host target gene. LOC255098 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255098, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255098 BINDING SITE, designated SEQ ID:45689, to the nucleotide sequence of VGAM373 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3084.

[18679] Another function of VGAM373 is therefore inhibition of LOC255098 (Accession XM\_170912). Accordingly, utilities of VGAM373 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255098. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 374 (VGAM374) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18680] VGAM374 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM374 was detected is described hereinabove with reference to Figs. 1–8.

[18681] VGAM374 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM374 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18682] VGAM374 gene encodes a VGAM374 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM374 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM374 precursor RNA is designated SEQ ID:360, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:360 is located at position 13667 relative to the genome of Avian Infectious Bronchitis Virus.

[18683] VGAM374 precursor RNA folds onto itself, forming VGAM374 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18684] An enzyme complex designated DICER COMPLEX, `dices` the VGAM374 folded precursor RNA into VGAM374 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 63%) nucleotide sequence of VGAM374 RNA is designated SEQ ID:3085, and is provided hereinbelow with reference to the sequence listing part.

[18685] VGAM374 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM374 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM374 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18686] VGAM374 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM374 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM374 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM374 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM374 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18687] The complementary binding of VGAM374 RNA, herein designated VGAM RNA, to host target binding sites on VGAM374 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM374 host target RNA into VGAM374 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18688] It is appreciated that VGAM374 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM374 host target genes. The mRNA of



each one of this plurality of VGAM374 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM374 RNA, herein designated VGAM RNA, and which when bound by VGAM374 RNA causes inhibition of translation of respective one or more VGAM374 host target proteins.

[18689] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM374 gene, herein designated VGAM GENE, on one or more VGAM374 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[18690] It is yet further appreciated that a function of VGAM374 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM374 correlate with, and may be deduced from, the identity of the host target genes which VGAM374 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18691] Nucleotide sequences of the VGAM374 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM374 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM374 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM374 are further described hereinbelow with reference to Table 1.

[18692] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM374 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM374 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[18693] As mentioned hereinabove with reference to Fig. 1, a function of VGAM374 gene, herein designated VGAM is inhibition of expression of VGAM374 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM374 correlate with, and may be deduced from, the identity of the target genes which VGAM374 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18694] Acid Phosphatase 1, Soluble (ACP1, Accession NM\_004300) is a VGAM374 host target gene. ACP1 BINDING SITE1 and ACP1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ACP1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACP1 BINDING SITE1 and ACP1 BINDING SITE2, designated SEQ ID:10510 and SEQ ID:13960 respectively, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18695] A function of VGAM374 is therefore inhibition of Acid

Phosphatase 1, Soluble (ACP1, Accession NM\_004300), a gene which as demonstrated in starch-gel electrophoresis. Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACP1. The function of ACP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. Heparanase (HPSE, Accession NM\_006665) is another VGAM374 host target gene. HPSE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HPSE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HPSE BINDING SITE, designated SEQ ID:13480, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18696] Another function of VGAM374 is therefore inhibition of Heparanase (HPSE, Accession NM\_006665), a gene which is an endoglycosidase that cleaves heparan sulfate. Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with HPSE. The function of HPSE has been established by previous studies. Heparanase is an endoglycosidase that cleaves heparan sulfate, an important component of the extracellular matrix and vascular basal lamina. The degradation of heparan sulfate by heparanase is a key step in the extravasation of tumor cells and migrating leukocytes, but is also important in physiologic processes including angiogenesis, wound healing, and smooth muscle proliferation. By sequential affinity chromatography of SV40-transformed embryonic lung fibroblasts, Toyoshima and Nakajima (1999) purified a 50-kD protein with heparanase activity. Hulett et al. (1999) and Vlodavsky et al. (1999) applied similar strategies to platelets and placenta, respectively. By searching EST databases, all 3 groups identified cDNAs encoding a 543-amino acid heparanase protein (HPSE) with 6 potential N-glycosylation sites. The protein also has putative hydrophobic stretches suggestive of signal peptides and a transmembrane protein (Hulett et al., 1999). Northern blot analysis revealed expression of a 2-kb transcript in placenta but not in heart, brain, lung, liver, skeletal muscle, kidney, or pancreas. A 4.4-kb transcript is expressed at low levels in all tissues. Both transcripts are expressed

equivalently in peripheral blood leukocytes, spleen, lymph node, bone marrow, fetal liver, and thymus (Hulett et al., 1999; Kussie et al., 1999). Functional analyses revealed that expression correlates with heparanase activity (Toyoshima and Nakajima, 1999; Vlodavsky et al. (1999); Hulett et al., 1999). RT/PCR, in situ hybridization, and functional analyses demonstrated a correlation of gene expression and heparanase activity with increased metastatic potential in breast cancer tissues and cell lines (Vlodavsky et al., 1999).

[18697] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18698] Baker, E.; Crawford, J.; Sutherland, G. R.; Freeman, C.; Parish, C. R.; Hulett, M. D. : Human HPA endoglycosidase heparanase. *Chromosome Res.* 7: 319 only, 1999. ; and

[18699] Hulett, M. D.; Freeman, C.; Hamdorf, B. J.; Baker, R. T.; Harris, M. J.; Parish, C. R. : Cloning of mammalian heparanase, an important enzyme in tumor invasion and metastasis. *Nature M.*

[18700] Further studies establishing the function and utilities of HPSE are found in John Hopkins OMIM database record ID 604724, and in cited publications numbered 4994–4998

listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Selectin L (lymphocyte adhesion molecule 1) (SELL, Accession NM\_000655) is another VGAM374 host target gene. SELL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SELL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SELL BINDING SITE, designated SEQ ID:6316, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18701] Another function of VGAM374 is therefore inhibition of Selectin L (lymphocyte adhesion molecule 1) (SELL, Accession NM\_000655), a gene which is a cell surface adhesion protein. Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SELL. The function of SELL has been established by previous studies. This glycoprotein was first identified in the mouse as the Mel-14 antigen, a lymph node homing receptor (Lnhr) also found on neutrophils and monocytes, by Lasky et al. (1989). In addition to lymphocyte homing, this molecule may play a role in

neutrophil adhesion to endothelium at sites of inflammation. The human counterpart was referred to as the LEU8/TQ1 antigen. The human homolog of mouse lymph node homing receptor was cloned by Siegelman and Weissman (1989). Distech et al. (1989) and Tedder et al. (1989) mapped the LYAM1 gene to 1q23–q25 by in situ hybridization. The gene for another member of the adhesion molecule family, SELP (OMIM Ref. No. 173610), is located in this same area. Indeed, Watson et al. (1990) demonstrated that these 2 genes and that for endothelial leukocyte adhesion molecule–1 (SELE; 131210) map to the same 300–kb segment. Furthermore, Watson et al. (1990) found that these 3 genes are closely situated on distal mouse chromosome 1 which is syntenic with human chromosome 1q; in 428 meiotic events, no crossovers were identified among these 3 genes and the gene for coagulation factor V (OMIM Ref. No. 227400). Dowbenko et al. (1991) also mapped the gene to a region of mouse chromosome 1, very near a site previously shown to contain the genes for the family of complement regulatory proteins. They found, furthermore, a correspondence between the domains of the protein and the coding exons of the gene. In the course of constructing a physical map of



1q, Oakey et al. (1992) positioned LYAM between ELAM and SELP and gave the location of all 3, as well as of F5 (OMIM Ref. No. 227400), as 1q23–q25.

[18702] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18703] Lasky, L. A.; Singer, M. S.; Yednock, T. A.; Dowbenko, D.; Fennie, C.; Rodriguez, H.; Nguyen, T.; Stachel, S.; Rosen, S. D. : Cloning of a lymphocyte homing receptor reveals a lectin domain. Cell 56: 1045–1055, 1989. ; and

[18704] Oakey, R. J.; Watson, M. L.; Seldin, M. F. : Construction of a physical map on mouse and human chromosome 1: comparison of 13 Mb of mouse and 11 Mb of human DNA. Hum. Molec. Genet. 1: 6.

[18705] Further studies establishing the function and utilities of SELL are found in John Hopkins OMIM database record ID 153240, and in cited publications numbered 11805, 11353, 11503–11504, 3934, 11505–1150 and 11810 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ10287 (Accession NM\_019083) is another VGAM374 host target gene. FLJ10287 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded

by FLJ10287, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10287 BINDING SITE, designated SEQ ID:21154, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18706] Another function of VGAM374 is therefore inhibition of FLJ10287 (Accession NM\_019083). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10287. Frequently Rearranged In Advanced T-cell Lymphomas (FRAT1, Accession NM\_005479) is another VGAM374 host target gene. FRAT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FRAT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FRAT1 BINDING SITE, designated SEQ ID:11982, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18707] Another function of VGAM374 is therefore inhibition of

Frequently Rearranged In Advanced T-cell Lymphomas (FRAT1, Accession NM\_005479). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FRAT1. KIAA1143 (Accession XM\_044014) is another VGAM374 host target gene. KIAA1143 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1143, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1143 BINDING SITE, designated SEQ ID:34070, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18708] Another function of VGAM374 is therefore inhibition of KIAA1143 (Accession XM\_044014). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1143. KIAA1283 (Accession XM\_050563) is another VGAM374 host target gene. KIAA1283 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1283, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1283 BINDING SITE, designated SEQ ID:35662, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18709] Another function of VGAM374 is therefore inhibition of KIAA1283 (Accession XM\_050563). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1283. KIAA1719 (Accession XM\_042936) is another VGAM374 host target gene. KIAA1719 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1719, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1719 BINDING SITE, designated SEQ ID:33816, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18710] Another function of VGAM374 is therefore inhibition of KIAA1719 (Accession XM\_042936). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1719. LIM and SH3 Protein 1 (LASP1, Accession NM\_006148) is another VGAM374 host target gene. LASP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LASP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LASP1 BINDING SITE, designated SEQ ID:12802, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18711] Another function of VGAM374 is therefore inhibition of LIM and SH3 Protein 1 (LASP1, Accession NM\_006148). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LASP1. MGC4707 (Accession NM\_024113) is another VGAM374 host target gene. MGC4707 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4707, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4707 BINDING SITE, designated SEQ ID:23564, to the nucleotide sequence of VGAM374 RNA, herein designated

VGAM RNA, also designated SEQ ID:3085.

[18712] Another function of VGAM374 is therefore inhibition of MGC4707 (Accession NM\_024113). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4707. LOC150139 (Accession XM\_086794) is another VGAM374 host target gene. LOC150139 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150139, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150139 BINDING SITE, designated SEQ ID:38860, to the nucleotide sequence of VGAM374 RNA, herein designated VGAM RNA, also designated SEQ ID:3085.

[18713] Another function of VGAM374 is therefore inhibition of LOC150139 (Accession XM\_086794). Accordingly, utilities of VGAM374 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150139. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 375 (VGAM375) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18714] VGAM375 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM375 was detected is described hereinabove with reference to Figs. 1–8.

[18715] VGAM375 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Avian Infectious Bronchitis Virus. VGAM375 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18716] VGAM375 gene encodes a VGAM375 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM375 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM375 precursor RNA is designated SEQ ID:361, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:361 is located at position 19796 relative to the genome of Avian Infectious Bronchitis Virus.

[18717] VGAM375 precursor RNA folds onto itself, forming

VGAM375 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18718] An enzyme complex designated DICER COMPLEX, `dices` the VGAM375 folded precursor RNA into VGAM375 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 54%) nucleotide sequence of VGAM375 RNA is designated SEQ ID:3086, and is provided hereinbelow with reference to the sequence listing part.

[18719] VGAM375 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM375 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM375 host target RNA comprises



three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[18720] VGAM375 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM375 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM375 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM375 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM375 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18721] The complementary binding of VGAM375 RNA, herein designated VGAM RNA, to host target binding sites on VGAM375 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM375 host target RNA into VGAM375 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18722] It is appreciated that VGAM375 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM375 host target genes. The mRNA of each one of this plurality of VGAM375 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM375 RNA, herein designated VGAM RNA, and which when bound by VGAM375 RNA causes inhibition of translation of respective one or more VGAM375 host target proteins.

[18723] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM375 gene, herein designated VGAM GENE, on one or more VGAM375 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18724] It is yet further appreciated that a function of VGAM375 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM375 include diagnosis, prevention and treatment of viral infection by Avian Infectious Bronchitis Virus. Specific functions, and accordingly utilities, of VGAM375 correlate with, and may be deduced from, the identity of the host target genes which VGAM375 binds

and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18725] Nucleotide sequences of the VGAM375 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM375 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM375 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM375 are further described hereinbelow with reference to Table 1.

[18726] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM375 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM375 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18727] As mentioned hereinabove with reference to Fig. 1, a function of VGAM375 gene, herein designated VGAM is inhibition of expression of VGAM375 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM375 correlate with, and may be deduced from, the identity of the target genes which VGAM375 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[18728] Nuclear Receptor Subfamily 5, Group A, Member 2 (NR5A2, Accession NM\_003822) is a VGAM375 host target gene. NR5A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NR5A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR5A2 BINDING SITE, designated SEQ ID:9916, to the nucleotide sequence of VGAM375 RNA, herein designated VGAM RNA, also designated SEQ ID:3086.

[18729] A function of VGAM375 is therefore inhibition of Nuclear Receptor Subfamily 5, Group A, Member 2 (NR5A2, Accession NM\_003822), a gene which is a member of nuclear receptor superfamily of transcriptional activators and activates the hepatitis B virus (HBV) promoter. Accordingly, utilities of VGAM375 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR5A2. The function of NR5A2 has been established by previous studies. By means of yeast one-hybrid screening of a liver cDNA library, Li et al. (1998) cloned a cDNA encoding a novel hepatocyte transcription factor,

which they called HB1F for human B1-binding factor. The deduced 495-amino acid protein, which has a molecular mass of 54 kD, belongs to the fushi tarazu factor-1 (OMIM Ref. No. FTZ-F1) subfamily of orphan nuclear receptors and is closely related to steroidogenic factor-1 (SF1; 184757), another member of this subfamily. HB1F contains a DNA-binding domain with 2 zinc finger motifs, an FTZ-F1 box, and a ligand-binding domain. Northern blot analysis revealed that HB1F is expressed in liver, pancreas, and lung as a 5.2-kb transcript. An additional transcript of 3.8 kb was present in hepatoma cells HepG2. The authors identified 2 HB1F isoforms which differ in their A/B region. HB1F specifically binds and activates viral hepatitis B enhancer II, an essential element for the liver-specific regulation of hepatitis B virus gene expression.

Cholesterol 7- $\alpha$ -hydroxylase is the first and rate-limiting enzyme in a pathway through which cholesterol is metabolized to bile acids. The gene encoding cholesterol 7- $\alpha$ -hydroxylase, CYP7A (OMIM Ref. No. 118455), is expressed exclusively in the liver. Overexpression of CYP7A in hamsters results in reduction of serum cholesterol levels, suggesting that the enzyme plays a central role in cholesterol homeostasis. Nitta et al. (1999) re-

ported the identification of a liver-specific transcription factor that binds to the promoter of the human CYP7A gene. They designated this factor CPF for 'CYP7A promoter-binding factor' and identified it as a human homolog of the *Drosophila* orphan nuclear receptor fushi tarazu F1 (OMIM Ref. No. Ftz-F1). Nitta et al. (1999) isolated a CPF cDNA encoding a 495-amino acid protein from a human liver cDNA library. They found evidence for 2 CPF variants derived from alternative splicing. Northern blot analysis detected enriched expression in pancreas and liver, with a low level of expression in heart and lung. Mutation of the CPF binding site within the CYP7A promoter abolished liver-specific expression of the gene in transient transfection assays. Cotransfection of a CPF expression plasmid and a CYP7A reporter gene resulted in specific induction of CYP7A-directed transcription. These observations suggested that CPF is a key regulator of human CYP7A gene expression in the liver.

[18730] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18731] Li, M.; Xie, Y.-H.; Kong, Y.-Y.; Wu, X.; Zhu, L.; Wang, Y. : Cloning and characterization of a novel human hepatocyte

transcription factor, hB1F, which binds and activates enhancer II of hepatitis B virus. J. Biol. Chem. 273: 29022–29031, 1998. ; and

[18732] Nitta, M.; Ku, S.; Brown, C.; Okamoto, A. Y.; Shan, B. : CPF: an orphan nuclear receptor that regulates liver-specific expression of the human cholesterol 7- $\alpha$ -hydroxylase gene. Proc.

[18733] Further studies establishing the function and utilities of NR5A2 are found in John Hopkins OMIM database record ID 604453, and in cited publications numbered 4762, 12136, 594 and 12138 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CXYorf1 (Accession XM\_088704) is another VGAM375 host target gene. CXYorf1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CXYorf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CXYorf1 BINDING SITE, designated SEQ ID:39908, to the nucleotide sequence of VGAM375 RNA, herein designated VGAM RNA, also designated SEQ ID:3086.

[18734] Another function of VGAM375 is therefore inhibition of



CXYorf1 (Accession XM\_088704). Accordingly, utilities of VGAM375 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CXYorf1. DKFZP434L0718 (Accession NM\_032139) is another VGAM375 host target gene. DKFZP434L0718 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP434L0718, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434L0718 BINDING SITE, designated SEQ ID:25820, to the nucleotide sequence of VGAM375 RNA, herein designated VGAM RNA, also designated SEQ ID:3086.

[18735] Another function of VGAM375 is therefore inhibition of DKFZP434L0718 (Accession NM\_032139). Accordingly, utilities of VGAM375 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434L0718. FLJ21302 (Accession NM\_022901) is another VGAM375 host target gene. FLJ21302 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ21302, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21302 BINDING SITE, designated SEQ ID:23183, to the nucleotide sequence of VGAM375 RNA, herein designated VGAM RNA, also designated SEQ ID:3086.

[18736] Another function of VGAM375 is therefore inhibition of FLJ21302 (Accession NM\_022901). Accordingly, utilities of VGAM375 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21302. LOC200093 (Accession XM\_032184) is another VGAM375 host target gene. LOC200093 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200093, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200093 BINDING SITE, designated SEQ ID:31600, to the nucleotide sequence of VGAM375 RNA, herein designated VGAM RNA, also designated SEQ ID:3086.

[18737] Another function of VGAM375 is therefore inhibition of LOC200093 (Accession XM\_032184). Accordingly, utilities of VGAM375 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC200093. LOC91040 (Accession XM\_035641) is another VGAM375 host target gene. LOC91040 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91040 BINDING SITE, designated SEQ ID:32317, to the nucleotide sequence of VGAM375 RNA, herein designated VGAM RNA, also designated SEQ ID:3086.

[18738] Another function of VGAM375 is therefore inhibition of LOC91040 (Accession XM\_035641). Accordingly, utilities of VGAM375 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91040. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 376 (VGAM376) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18739] VGAM376 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM376 was detected is described hereinabove with reference to Figs. 1–8.

[18740] VGAM376 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Eggplant Mosaic Virus. VGAM376 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18741] VGAM376 gene encodes a VGAM376 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM376 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM376 precursor RNA is designated SEQ ID:362, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:362 is located at position 1184 relative to the genome of Eggplant Mosaic Virus.

[18742] VGAM376 precursor RNA folds onto itself, forming VGAM376 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18743] An enzyme complex designated DICER COMPLEX, `dices` the VGAM376 folded precursor RNA into VGAM376 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM376 RNA is designated SEQ ID:3087, and is provided hereinbelow with reference to the sequence listing part.

[18744] VGAM376 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM376 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM376 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18745] VGAM376 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM376 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM376 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM376 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM376 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[18746] The complementary binding of VGAM376 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM376 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM376 host target RNA into VGAM376 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18747] It is appreciated that VGAM376 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM376 host target genes. The mRNA of each one of this plurality of VGAM376 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM376 RNA, herein designated VGAM RNA, and which when bound by VGAM376 RNA causes inhibition of translation of respective one or more VGAM376 host target proteins.

[18748] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM376 gene, herein designated VGAM GENE, on one or more VGAM376 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18749] It is yet further appreciated that a function of VGAM376 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of viral infection by Eggplant Mosaic Virus. Specific functions, and accordingly utilities, of VGAM376 correlate with, and may be deduced from, the identity of the host target genes which VGAM376 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18750] Nucleotide sequences of the VGAM376 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM376 RNA, herein designated VGAM RNA,



and a schematic representation of the secondary folding of VGAM376 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM376 are further described hereinbelow with reference to Table 1.

[18751] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM376 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM376 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18752] As mentioned hereinabove with reference to Fig. 1, a function of VGAM376 gene, herein designated VGAM is inhibition of expression of VGAM376 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM376 correlate with, and may be deduced from, the identity of the target genes which VGAM376 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18753] G Protein-coupled Receptor 48 (GPR48, Accession NM\_018490) is a VGAM376 host target gene. GPR48 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GPR48, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR48 BINDING SITE, designated SEQ ID:20550, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18754] A function of VGAM376 is therefore inhibition of G Protein-coupled Receptor 48 (GPR48, Accession NM\_018490), a gene which binds to follicle-stimulating hormone and thyroid-stimulating hormone. Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR48. The function of GPR48 has been established by previous studies. By EST database searching with known GPCRs as queries, Hsu et al. (1998) identified ESTs encoding transmembrane domains 4 and 5 of human GPR48, which they called LGR4. By RT-PCR and repeated screening of a rat ovary cDNA library, they isolated a full-length cDNA encoding rat Lgr4. Sequence analysis predicted that the 951-amino acid rat Lgr4 protein contains a signal peptide; N- and C-flanking cysteine-rich sequences separated by 17 LRRs; 5 potential N-glycosylation sites; a transmembrane region; and a 145-residue cytoplasmic

tail with multiple phosphorylation sites and a conserved potential protein kinase A (see OMIM Ref. No. 176911) phosphorylation site. Northern blot analysis of human tissues detected a 5.5-kb LGR4 transcript in multiple steroidogenic tissues and in a number of other tissues. Functional analysis showed that expression of a chimeric receptor composed of the extracellular domain of luteinizing hormone receptor (OMIM Ref. No. 152790) with the transmembrane and cytoplasmic domains of Lgr4 resulted in binding of hCG (OMIM Ref. No. 118860) but no increase in basal production of cAMP, suggesting that LGR4 may signal through another mechanism. Loh et al. (2001) cloned human GPR48. Like rat Lgr4, the deduced human GPR48 protein has 951 amino acids and a similar structure. Northern blot analysis detected wide expression of GPR48 that was highest in pancreas. Within brain, highest expression of GPR48 was in hippocampus and amygdala. Expression of Gpr48 in mouse embryos occurred as early as embryonic day 7 and peaked at day 15.

[18755] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18756] Hsu, S. Y.; Liang, S.-G.; Hsueh, A. J. W. : Characterization

of two LGR genes homologous to gonadotropin and thyrotropin receptors with extracellular leucine-rich repeats and a G protein-coupled, seven-transmembrane region. Molec. Endocr. 12: 1830-1845, 1998. ; and

[18757] Loh, E. D.; Broussard, S. R.; Kolakowski, L. F. : Molecular characterization of a novel glycoprotein hormone G-protein-coupled receptor. Biochem. Biophys. Res. Commun. 282: 757-764, 2001.

[18758] Further studies establishing the function and utilities of GPR48 are found in John Hopkins OMIM database record ID 606666, and in cited publications numbered 6451-6453 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Mature T-cell Proliferation 1 (MTCP1, Accession NM\_014221) is another VGAM376 host target gene. MTCP1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MTCP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTCP1 BINDING SITE, designated SEQ ID:15487, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18759] Another function of VGAM376 is therefore inhibition of Mature T-cell Proliferation 1 (MTCP1, Accession NM\_014221). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTCP1. Nuclear Protein, Ataxia-telangiectasia Locus (NPAT, Accession XM\_040846) is another VGAM376 host target gene. NPAT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NPAT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NPAT BINDING SITE, designated SEQ ID:33386, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18760] Another function of VGAM376 is therefore inhibition of Nuclear Protein, Ataxia-telangiectasia Locus (NPAT, Accession XM\_040846), a gene which is expressed in all tissues. Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NPAT. The function of NPAT has been established by previous studies. From the region of the ataxia-telangiectasia gene (ATM; 208900) on

11q22–q23, Imai et al. (1996) identified a new gene, which they designated NPAT. The gene lies only 0.5 kb from the 5–prime end of the ATM gene and is transcribed in the opposite direction as ATM. The gene encodes a 1,427–amino acid protein containing nuclear localization signals and target sites for phosphorylation by cyclin–dependent protein kinases associated with E2F (see OMIM Ref. No. 189971). NPAT has a calculated molecular mass of 154,300 Da. It is relatively serine and threonine rich. The mRNA of NPAT was detected in all human tissues examined and its genomic sequence was strongly conserved through eukaryotes, suggesting that the NPAT gene may be essential for cell maintenance, i.e., a housekeeping gene. Imai et al. (1996) proposed that the promoter region may be shared by ATM and NPAT and that each gene may influence the expression of the other. They stated that they had identified no mutations of NPAT in 8 Japanese ataxia–telangiectasia patients. Byrd et al. (1996) identified a gene, which they designated E14, as a novel open reading frame in close proximity to the 5–prime end of the ATM gene. The E14 gene is transcribed divergently from a promoter region that it shares with ATM. The authors estimated that the complete E14 gene is more than

55 kb in length. They described its exon/intron boundaries; exon 13 is 1,653 bp long and comprises over a third of the coding sequence. Byrd et al. (1996) found that the gene is ubiquitously expressed. They detected 3 mRNA species: the most abundant transcript was 6.25 kb and the less abundant transcripts were 8.8 kb and 5.3 kb. They proposed that the 2 most abundant species resulted from the use of alternative poly(A) signals. Byrd et al. (1996) reported that serine and threonine residues comprise 21% of the E14 protein. Their studies demonstrated that the E14/ATM intergenic region functions as a bidirectional promoter. From studies of 5 ataxia-telangiectasia patients, Byrd et al. (1996) obtained no evidence for mutations in the E14 coding or promoter regions.

[18761] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18762] Byrd, P. J.; Cooper, P. R.; Stankovic, T.; Kullar, H. S.; Watts, G. D. J.; Robinson, P. J.; Taylor, M. R. : A gene transcribed from the bidirectional ATM promoter coding for a serine rich protein: amino acid sequence, structure and expression studies. *Hum. Molec. Genet.* 5: 1785–1791, 1996. ; and

[18763] Imai, T.; Yamauchi, M.; Seki, N.; Sugawara, T.; Saito, T.; Matsuda, Y.; Ito, H.; Nagase, T.; Nomura, N.; Hori, T. : Identification and characterization of a new gene physically linked t.

[18764] Further studies establishing the function and utilities of NPAT are found in John Hopkins OMIM database record ID 601448, and in cited publications numbered 9637, 9638–9641, 132 and 1352 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Family 12 (potassium/chloride transporters), Member 7 (SLC12A7, Accession NM\_006598) is another VGAM376 host target gene. SLC12A7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC12A7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC12A7 BINDING SITE, designated SEQ ID:13376, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18765] Another function of VGAM376 is therefore inhibition of Solute Carrier Family 12 (potassium/chloride trans–



porters), Member 7 (SLC12A7, Accession NM\_006598), a gene which is a potassium/chloride-cotransporter. Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC12A7. The function of SLC12A7 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200. Wingless-type MMTV Integration Site Family, Member 3A (WNT3A, Accession NM\_033131) is another VGAM376 host target gene. WNT3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WNT3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WNT3A BINDING SITE, designated SEQ ID:26975, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18766] Another function of VGAM376 is therefore inhibition of Wingless-type MMTV Integration Site Family, Member 3A (WNT3A, Accession NM\_033131). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with WNT3A. Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698) is another VGAM376 host target gene. BLCAP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by BLCAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLCAP BINDING SITE, designated SEQ ID:13522, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18767] Another function of VGAM376 is therefore inhibition of Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLCAP. Calcium Binding Protein 5 (CABP5, Accession NM\_019855) is another VGAM376 host target gene. CABP5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CABP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CABP5 BINDING SITE,

designated SEQ ID:21260, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18768] Another function of VGAM376 is therefore inhibition of Calcium Binding Protein 5 (CABP5, Accession NM\_019855). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CABP5. FLJ12425 (Accession XM\_098290) is another VGAM376 host target gene. FLJ12425 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12425, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12425 BINDING SITE, designated SEQ ID:41564, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18769] Another function of VGAM376 is therefore inhibition of FLJ12425 (Accession XM\_098290). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12425. KIAA1981 (Accession XM\_114000) is another VGAM376

host target gene. KIAA1981 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1981, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1981 BINDING SITE, designated SEQ ID:42610, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18770] Another function of VGAM376 is therefore inhibition of KIAA1981 (Accession XM\_114000). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1981. PSR (Accession XM\_036784) is another VGAM376 host target gene. PSR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSR BINDING SITE, designated SEQ ID:32502, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18771] Another function of VGAM376 is therefore inhibition of PSR (Accession XM\_036784). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSR. SCYB11 (Accession XM\_113426) is another VGAM376 host target gene. SCYB11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCYB11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCYB11 BINDING SITE, designated SEQ ID:42260, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18772] Another function of VGAM376 is therefore inhibition of SCYB11 (Accession XM\_113426). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCYB11. SMOC2 (Accession XM\_051452) is another VGAM376 host target gene. SMOC2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SMOC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BIND-

ING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMOC2 BINDING SITE, designated SEQ ID:35836, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18773] Another function of VGAM376 is therefore inhibition of SMOC2 (Accession XM\_051452). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMOC2. Signal Transducer and Activator of Transcription 2, 113kDa (STAT2, Accession NM\_005419) is another VGAM376 host target gene. STAT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STAT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAT2 BINDING SITE, designated SEQ ID:11893, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18774] Another function of VGAM376 is therefore inhibition of Signal Transducer and Activator of Transcription 2, 113kDa (STAT2, Accession NM\_005419). Accordingly,

utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAT2. VI (Accession NM\_013443) is another VGAM376 host target gene. VI BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VI, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VI BINDING SITE, designated SEQ ID:15109, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18775] Another function of VGAM376 is therefore inhibition of VI (Accession NM\_013443). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VI. Zinc Finger Protein 238 (ZNF238, Accession NM\_006352) is another VGAM376 host target gene. ZNF238 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF238, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF238

BINDING SITE, designated SEQ ID:13047, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18776] Another function of VGAM376 is therefore inhibition of Zinc Finger Protein 238 (ZNF238, Accession NM\_006352). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF238. LOC125228 (Accession XM\_058913) is another VGAM376 host target gene. LOC125228 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC125228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC125228 BINDING SITE, designated SEQ ID:36793, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18777] Another function of VGAM376 is therefore inhibition of LOC125228 (Accession XM\_058913). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125228. LOC147671 (Accession XM\_085844) is an-



other VGAM376 host target gene. LOC147671 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147671, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147671 BINDING SITE, designated SEQ ID:38378, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18778] Another function of VGAM376 is therefore inhibition of LOC147671 (Accession XM\_085844). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147671. LOC158563 (Accession XM\_088606) is another VGAM376 host target gene. LOC158563 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158563, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158563 BINDING SITE, designated SEQ ID:39869, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18779] Another function of VGAM376 is therefore inhibition of LOC158563 (Accession XM\_088606). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158563. LOC197285 (Accession XM\_113752) is another VGAM376 host target gene. LOC197285 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197285, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197285 BINDING SITE, designated SEQ ID:42416, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18780] Another function of VGAM376 is therefore inhibition of LOC197285 (Accession XM\_113752). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197285. LOC221839 (Accession XM\_166506) is another VGAM376 host target gene. LOC221839 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221839, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221839 BINDING SITE, designated SEQ ID:44431, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18781] Another function of VGAM376 is therefore inhibition of LOC221839 (Accession XM\_166506). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221839. LOC90092 (Accession XM\_028862) is another VGAM376 host target gene. LOC90092 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90092, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90092 BINDING SITE, designated SEQ ID:30790, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18782] Another function of VGAM376 is therefore inhibition of LOC90092 (Accession XM\_028862). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC90092. LOC91252 (Accession XM\_037173) is another VGAM376 host target gene. LOC91252 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91252, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91252 BINDING SITE, designated SEQ ID:32555, to the nucleotide sequence of VGAM376 RNA, herein designated VGAM RNA, also designated SEQ ID:3087.

[18783] Another function of VGAM376 is therefore inhibition of LOC91252 (Accession XM\_037173). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91252. LOC91960 (Accession XM\_041872) is another VGAM376 host target gene. LOC91960 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91960, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91960 BINDING SITE, designated SEQ ID:33615, to the nucleotide sequence of VGAM376 RNA, herein designated

VGAM RNA, also designated SEQ ID:3087.

[18784] Another function of VGAM376 is therefore inhibition of LOC91960 (Accession XM\_041872). Accordingly, utilities of VGAM376 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91960. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 377 (VGAM377) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18785] VGAM377 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM377 was detected is described hereinabove with reference to Figs. 1–8.

[18786] VGAM377 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Eggplant Mosaic Virus. VGAM377 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18787] VGAM377 gene encodes a VGAM377 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM377 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM377 precursor RNA is designated SEQ ID:363, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:363 is located at position 2809 relative to the genome of Eggplant Mosaic Virus.

[18788] VGAM377 precursor RNA folds onto itself, forming VGAM377 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18789] An enzyme complex designated DICER COMPLEX, `dices` the VGAM377 folded precursor RNA into VGAM377 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM377 RNA is designated SEQ ID:3088, and is provided hereinbelow with reference to the sequence listing part.

[18790] VGAM377 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM377 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM377 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18791] VGAM377 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM377 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM377 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM377 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM377 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18792] The complementary binding of VGAM377 RNA, herein designated VGAM RNA, to host target binding sites on VGAM377 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM377 host target RNA into VGAM377 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18793] It is appreciated that VGAM377 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM377 host target genes. The mRNA of



each one of this plurality of VGAM377 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM377 RNA, herein designated VGAM RNA, and which when bound by VGAM377 RNA causes inhibition of translation of respective one or more VGAM377 host target proteins.

[18794] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM377 gene, herein designated VGAM GENE, on one or more VGAM377 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[18795] It is yet further appreciated that a function of VGAM377 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of viral infection by Eggplant Mosaic Virus. Specific functions, and accordingly utilities, of VGAM377 correlate with, and may be deduced from, the identity of the host target genes which VGAM377 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18796] Nucleotide sequences of the VGAM377 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM377 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM377 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM377 are further described hereinbelow with reference to Table 1.

[18797] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM377 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM377 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[18798] As mentioned hereinabove with reference to Fig. 1, a function of VGAM377 gene, herein designated VGAM is inhibition of expression of VGAM377 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM377 correlate with, and may be deduced from, the identity of the target genes which VGAM377 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18799] D12S2489E (Accession NM\_007360) is a VGAM377 host target gene. D12S2489E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by D12S2489E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of D12S2489E BINDING SITE, designated SEQ ID:14291, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18800] A function of VGAM377 is therefore inhibition of D12S2489E (Accession NM\_007360), a gene which interacts in the inhibition and activation of NK cells. Accord-

ingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with D12S2489E. The function of D12S2489E and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM156. Peroxisome Biogenesis Factor 10 (PEX10, Accession NM\_002617) is another VGAM377 host target gene. PEX10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PEX10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PEX10 BINDING SITE, designated SEQ ID:8480, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18801] Another function of VGAM377 is therefore inhibition of Peroxisome Biogenesis Factor 10 (PEX10, Accession NM\_002617). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PEX10. Syntrophin, Beta 1 (dystrophin-associated protein A1, 59kDa, basic component 1) (SNTB1, Accession NM\_021021) is another

VGAM377 host target gene. SNTB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SNTB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNTB1 BINDING SITE, designated SEQ ID:22013, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18802] Another function of VGAM377 is therefore inhibition of Syntrophin, Beta 1 (dystrophin-associated protein A1, 59kDa, basic component 1) (SNTB1, Accession NM\_021021). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNTB1. Cleavage and Polyadenylation Specific Factor 2, 100kDa (CPSF2, Accession XM\_029311) is another VGAM377 host target gene. CPSF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CPSF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CPSF2 BINDING SITE, designated SEQ

ID:30861, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18803] Another function of VGAM377 is therefore inhibition of Cleavage and Polyadenylation Specific Factor 2, 100kDa (CPSF2, Accession XM\_029311). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CPSF2. KIAA1183 (Accession XM\_031307) is another VGAM377 host target gene. KIAA1183 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1183, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1183 BINDING SITE, designated SEQ ID:31337, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18804] Another function of VGAM377 is therefore inhibition of KIAA1183 (Accession XM\_031307). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1183. Mitogen-activated Protein Kinase 6 (MAPK6,

Accession NM\_002748) is another VGAM377 host target gene. MAPK6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAPK6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPK6 BINDING SITE, designated SEQ ID:8626, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18805] Another function of VGAM377 is therefore inhibition of Mitogen-activated Protein Kinase 6 (MAPK6, Accession NM\_002748). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPK6. MGC21636 (Accession NM\_145032) is another VGAM377 host target gene. MGC21636 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC21636, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC21636 BINDING SITE, designated SEQ ID:29647, to the nucleotide sequence of

VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18806] Another function of VGAM377 is therefore inhibition of MGC21636 (Accession NM\_145032). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC21636. POPX1 (Accession NM\_014906) is another VGAM377 host target gene. POPX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POPX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POPX1 BINDING SITE, designated SEQ ID:17119, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18807] Another function of VGAM377 is therefore inhibition of POPX1 (Accession NM\_014906). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POPX1. WD Repeat Domain 9 (WDR9, Accession NM\_018963) is another VGAM377 host target gene. WDR9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by WDR9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WDR9 BINDING SITE, designated SEQ ID:21032, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18808] Another function of VGAM377 is therefore inhibition of WD Repeat Domain 9 (WDR9, Accession NM\_018963). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WDR9. LOC170217 (Accession XM\_093185) is another VGAM377 host target gene. LOC170217 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC170217, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170217 BINDING SITE, designated SEQ ID:40178, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18809] Another function of VGAM377 is therefore inhibition of LOC170217 (Accession XM\_093185). Accordingly, utilities

of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170217. LOC170218 (Accession XM\_093186) is another VGAM377 host target gene. LOC170218 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC170218, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170218 BINDING SITE, designated SEQ ID:40180, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18810] Another function of VGAM377 is therefore inhibition of LOC170218 (Accession XM\_093186). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170218. LOC170372 (Accession XM\_084317) is another VGAM377 host target gene. LOC170372 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC170372, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC170372 BINDING SITE, designated SEQ ID:37539, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18811] Another function of VGAM377 is therefore inhibition of LOC170372 (Accession XM\_084317). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170372. LOC219914 (Accession XM\_167788) is another VGAM377 host target gene. LOC219914 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219914, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219914 BINDING SITE, designated SEQ ID:44814, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18812] Another function of VGAM377 is therefore inhibition of LOC219914 (Accession XM\_167788). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219914. LOC91750 (Accession XM\_040376) is another VGAM377 host target gene. LOC91750 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC91750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91750 BINDING SITE, designated SEQ ID:33288, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18813] Another function of VGAM377 is therefore inhibition of LOC91750 (Accession XM\_040376). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91750. LOC92096 (Accession XM\_042812) is another VGAM377 host target gene. LOC92096 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC92096, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92096 BINDING SITE, designated SEQ ID:33775, to the nucleotide sequence of VGAM377 RNA, herein designated VGAM RNA, also designated SEQ ID:3088.

[18814] Another function of VGAM377 is therefore inhibition of

LOC92096 (Accession XM\_042812). Accordingly, utilities of VGAM377 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92096. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 378 (VGAM378) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18815] VGAM378 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM378 was detected is described hereinabove with reference to Figs. 1–8.

[18816] VGAM378 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Feline Immunodeficiency Virus. VGAM378 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18817] VGAM378 gene encodes a VGAM378 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM378 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM378 precursor RNA is designated SEQ ID:364, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:364 is located at position 7329 relative to the genome of Feline Immunodeficiency Virus.

[18818] VGAM378 precursor RNA folds onto itself, forming VGAM378 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18819] An enzyme complex designated DICER COMPLEX, `dices` the VGAM378 folded precursor RNA into VGAM378 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide se-

quence of VGAM378 RNA is designated SEQ ID:3089, and is provided hereinbelow with reference to the sequence listing part.

[18820] VGAM378 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM378 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM378 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18821] VGAM378 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM378 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM378 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM378 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM378 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[18822] The complementary binding of VGAM378 RNA, herein designated VGAM RNA, to host target binding sites on VGAM378 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM378 host target RNA into VGAM378 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18823] It is appreciated that VGAM378 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM378 host target genes. The mRNA of each one of this plurality of VGAM378 host target genes comprises one or more host target binding sites, each



having a nucleotide sequence which is at least partly complementary to VGAM378 RNA, herein designated VGAM RNA, and which when bound by VGAM378 RNA causes inhibition of translation of respective one or more VGAM378 host target proteins.

[18824] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM378 gene, herein designated VGAM GENE, on one or more VGAM378 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18825] It is yet further appreciated that a function of VGAM378 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM378 include diagnosis, prevention and treatment of viral infection by Feline Immunodeficiency Virus. Specific functions, and accordingly utilities, of VGAM378 correlate with, and may be deduced from, the identity of the host target genes which VGAM378 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18826] Nucleotide sequences of the VGAM378 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM378 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM378 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM378 are further described hereinbelow with reference to Table 1.

[18827] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM378 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM378 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18828] As mentioned hereinabove with reference to Fig. 1, a function of VGAM378 gene, herein designated VGAM is inhibition of expression of VGAM378 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM378 correlate with, and may be deduced from, the identity of the target genes which VGAM378 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18829] IMPACT (Accession NM\_018439) is a VGAM378 host target gene. IMPACT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IMPACT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IMPACT BINDING SITE, designated SEQ ID:20501, to the nucleotide sequence of VGAM378 RNA, herein designated VGAM RNA, also designated SEQ ID:3089.

[18830] A function of VGAM378 is therefore inhibition of IMPACT (Accession NM\_018439). Accordingly, utilities of VGAM378 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IMPACT. Fig. 1 further provides a conceptual description of a novel

bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 379 (VGAM379) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18831] VGAM379 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM379 was detected is described hereinabove with reference to Figs. 1–8.

[18832] VGAM379 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Feline Immunodeficiency Virus. VGAM379 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18833] VGAM379 gene encodes a VGAM379 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM379 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM379 precursor RNA is designated SEQ ID:365, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:365 is located at position 7178 relative to the genome of Feline

## Immunodeficiency Virus.

[18834] VGAM379 precursor RNA folds onto itself, forming VGAM379 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18835] An enzyme complex designated DICER COMPLEX, `dices` the VGAM379 folded precursor RNA into VGAM379 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM379 RNA is designated SEQ ID:3090, and is provided hereinbelow with reference to the sequence listing part.

[18836] VGAM379 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM379 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM379 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18837] VGAM379 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM379 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM379 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM379 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM379 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[18838] The complementary binding of VGAM379 RNA, herein designated VGAM RNA, to host target binding sites on VGAM379 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM379 host target RNA into VGAM379 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18839] It is appreciated that VGAM379 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM379 host target genes. The mRNA of each one of this plurality of VGAM379 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM379 RNA, herein designated VGAM RNA, and which when bound by VGAM379 RNA causes inhibition of translation of respective one or more VGAM379 host target proteins.

[18840] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM379 gene, herein designated VGAM GENE, on one or more VGAM379 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18841] It is yet further appreciated that a function of VGAM379 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of viral infection by Feline Immunodeficiency Virus. Specific functions, and accordingly utilities, of



VGAM379 correlate with, and may be deduced from, the identity of the host target genes which VGAM379 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18842] Nucleotide sequences of the VGAM379 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM379 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM379 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM379 are further described hereinbelow with reference to Table 1.

[18843] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM379 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM379 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18844] As mentioned hereinabove with reference to Fig. 1, a function of VGAM379 gene, herein designated VGAM is inhibition of expression of VGAM379 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM379 correlate with, and may be deduced

from, the identity of the target genes which VGAM379 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18845] Guanylate Cyclase 1, Soluble, Beta 2 (GUCY1B2, Accession NM\_004129) is a VGAM379 host target gene. GUCY1B2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GUCY1B2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GUCY1B2 BINDING SITE, designated SEQ ID:10335, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18846] A function of VGAM379 is therefore inhibition of Guanylate Cyclase 1, Soluble, Beta 2 (GUCY1B2, Accession NM\_004129), a gene which is beta 2 subunit of soluble guanylate cyclase which converts GTP into the second messenger cGMP and plays a major role in the cardiovascular system as a receptor for nitric oxide. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GUCY1B2. The function of GUCY1B2 has been estab-

lished by previous studies. Nitric oxide-sensitive guanylyl cyclase (EC 4.6.1.2) is a heterodimeric enzyme consisting of an alpha and a beta subunit. The enzyme converts GTP into the second messenger cGMP and plays a major role in the cardiovascular system as a receptor for nitric oxide. Yuen et al. (1990) isolated rat cDNAs encoding a guanylyl cyclase beta-subunit that they designated GCS-beta-2. The predicted 682-amino acid rat protein shares 27% identity with rat GCS-beta-1 (GUCY1B3; 139397). Unlike other guanylyl cyclases, GCS-beta-2 contains an 86-amino acid C-terminal extension with a consensus sequence for isoprenylation/carboxymethylation. Northern blot analysis indicated that GCS-beta-2 is expressed at higher levels in rat kidney and liver, whereas GCS-beta-1 is preferentially expressed in lung and brain. By PCR with primers based on the sequence of rat GCS-beta-2, Behrends et al. (1999) isolated a partial human heart GUCY1B2 cDNA. By fluorescence in situ hybridization and by linkage, Behrends et al. (1999) mapped the GUCY1B2 gene to 13q14.3. By in situ hybridization, Malterer et al. (1999) confirmed the assignment of the GUCY1B2 gene to 13q14.2-q14.3.

[18847] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [18848] Yuen, P. S. T.; Potter, L. R.; Garbers, D. L. : A new form of guanylyl cyclase is preferentially expressed in rat kidney. *Biochemistry* 29: 10872–10878, 1990. ; and
- [18849] Behrends, S.; Kazmierczak, B.; Steenpass, A.; Knauf, B.; Bullerdiek, J.; Scholz, H.; Eiberg, H. : Assignment of GUCY1B2, the gene coding for the beta-2 subunit of human guanylyl cyclase.
- [18850] Further studies establishing the function and utilities of GUCY1B2 are found in John Hopkins OMIM database record ID 603695, and in cited publications numbered 4954–4956 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Myotubularin Related Protein 8 (MTMR8, Accession NM\_015458) is another VGAM379 host target gene. MTMR8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MTMR8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTMR8 BINDING SITE, designated SEQ ID:17744, to the nucleotide sequence of VGAM379 RNA,

herein designated VGAM RNA, also designated SEQ ID:3090.

[18851] Another function of VGAM379 is therefore inhibition of Myotubularin Related Protein 8 (MTMR8, Accession NM\_015458), a gene which could be a tyrosine-phosphatase. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTMR8. The function of MTMR8 has been established by previous studies. MTMR8 encodes a myotubularin-related protein that, unlike most other members of the myotubularin-related protein family, has no dual-specificity phosphatase domain.

[18852] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18853] Appel, S.; Filter, M.; Reis, A.; Hennies, H. C.; Bergheim, A.; Ogilvie, E.; Arndt, S.; Simmons, A.; Lovett, M.; Hide, W.; Ramsay, M.; Reichwald, K.; Zimmermann, W.; Rosenthal, A. : Physical and transcriptional map of the critical region for keratolytic winter erythema (KWE) on chromosome 8p22-p23 between D8S550 and D8S1759. *Europ. J. Hum. Genet.* 10: 17-25, 2002. ; and

[18854] Appel, S.; Reichwald, K.; Zimmermann, W.; Reis, A.;

Rosenthal, A.; Hennies, H. C. : Identification and localization of a new human myotubularin-related protein gene, MTMR8, on 8p22-p23.

[18855] Further studies establishing the function and utilities of MTMR8 are found in John Hopkins OMIM database record ID 606260, and in cited publications numbered 11474-90 and 1264 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. 5-methyltetrahydrofolate-homocysteine Methyltransferase (MTR, Accession NM\_000254) is another VGAM379 host target gene. MTR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MTR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTR BINDING SITE, designated SEQ ID:5797, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18856] Another function of VGAM379 is therefore inhibition of 5-methyltetrahydrofolate-homocysteine Methyltransferase (MTR, Accession NM\_000254). Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with MTR. RNTRE (Accession NM\_014688) is another VGAM379 host target gene. RNTRE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNTRE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNTRE BINDING SITE, designated SEQ ID:16190, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18857] Another function of VGAM379 is therefore inhibition of RNTRE (Accession NM\_014688), a gene which may be involved in cell proliferation. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNTRE. The function of RNTRE has been established by previous studies. Matoskova et al. (1996) demonstrated that the product of the RNTRE gene is a 97- to 100-kD protein that stably associates in vivo and in vitro with EPS8 via the SH3 domain of the latter. In vitro, RNTRE displayed remarkable preference for binding to the SH3 domain of EPS8, compared with 8 other SH3s. A C-terminal trun-

cated mutant of RNTRE was able to confer proliferative advantage and reduced serum requirement to NIH3T3 fibroblasts, suggesting a role for RNTRE in cell proliferation. Epidermal growth factor receptor (EGFR; 131550) signaling involves small GTPases of the Rho family, and EGFR trafficking involves small GTPases of the Rab family. Lanzetti et al. (2000) reported that the EPS8 protein connects these signaling pathways. EPS8 is a substrate of EGFR that is held in a complex with SOS1 (OMIM Ref. No. 182530) by the adaptor protein E3B1 (OMIM Ref. No. 603050), thereby mediating activation of RAC (OMIM Ref. No. 602048). Through its SH3 domain, EPS8 interacts with RNTRE. Lanzetti et al. (2000) showed that RNTRE is a RAB5 (OMIM Ref. No. 179512) GTPase-activating protein (GAP) whose activity is regulated by EGFR. By entering in a complex with EPS8, RNTRE acts on RAB5 and inhibits internalization of the EGFR. Furthermore, RNTRE diverts EPS8 from its RAC-activating function, resulting in the attenuation of RAC signaling. Thus, depending on its state of association with E3B1 or RNTRE, EPS8 participates in both EGFR signaling through RAC and EGFR trafficking through RAB5. Lanzetti et al. (2000) showed that 2 arginine residues (arg106 and arg150 of RNTRE) are highly conserved in



TRH domains. In addition, an aspartate residue (asp147 of RNTRE) is invariant. Mutations of any of these residues to alanine resulted in proteins that were unable to display GAP activity on RAB5.

[18858] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18859] Lanzetti, L.; Rybin, V.; Malabarba, M. G.; Christoforidis, S.; Scita, G.; Zerial, M.; Di Fiore, P. P. : The Eps8 protein coordinates EGF receptor signalling through Rac and trafficking through Rab5. *Nature* 408: 374–377, 2000. ; and

[18860] Matoskova, B.; Wong, W. T.; Seki, N.; Nagase, T.; Nomura, N.; Robbins, K. C.; Di Fiore, P. P. : RN-tre identifies a family of tre-related proteins displaying a novel potential protein bind.

[18861] Further studies establishing the function and utilities of RNTRE are found in John Hopkins OMIM database record ID 605405, and in cited publications numbered 375, 7417–741 and 8361 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RP42 (Accession NM\_020640) is another VGAM379 host target gene. RP42 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA

encoded by RP42, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RP42 BINDING SITE, designated SEQ ID:21804, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18862] Another function of VGAM379 is therefore inhibition of RP42 (Accession NM\_020640), a gene which not clear yet. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RP42. The function of RP42 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM47. Secreted Frizzled-related Protein 1 (SFRP1, Accession NM\_003012) is another VGAM379 host target gene. SFRP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRP1 BINDING SITE, designated SEQ ID:8933, to the nucleotide sequence of

VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18863] Another function of VGAM379 is therefore inhibition of Secreted Frizzled-related Protein 1 (SFRP1, Accession NM\_003012), a gene which is a receptor for wnt proteins that may have an anti-apoptotic function. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRP1. The function of SFRP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM250.Splicing Factor, Arginine/serine-rich 1 (splicing factor 2, alternate splicing factor) (SFRS1, Accession NM\_006924) is another VGAM379 host target gene. SFRS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRS1 BINDING SITE, designated SEQ ID:13804, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18864] Another function of VGAM379 is therefore inhibition of Splicing Factor, Arginine/serine-rich 1 (splicing factor 2, alternate splicing factor) (SFRS1, Accession NM\_006924), a gene which plays an essential role in pre-mRNA splicing. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRS1. The function of SFRS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM323. Transcription Factor AP-2 Gamma (activating enhancer binding protein 2 gamma) (TFAP2C, Accession NM\_003222) is another VGAM379 host target gene. TFAP2C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TFAP2C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TFAP2C BINDING SITE, designated SEQ ID:9222, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18865] Another function of VGAM379 is therefore inhibition of Transcription Factor AP-2 Gamma (activating enhancer

binding protein 2 gamma) (TFAP2C, Accession NM\_003222), a gene which is a sequence-specific dna-binding protein that interacts with inducible viral and cellular enhancer elements to regulate transcription of selected genes. Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TFAP2C. The function of TFAP2C has been established by previous studies. Families of related transcription factors are often expressed in the same cell lineages but at different times or sites in the developing embryo. The AP-2 family appears to regulate the expression of genes required for development of tissues of ectodermal origin such as neural crest and skin (Williamson et al., 1996). AP-2 may also be involved in the overexpression of c-erbB-2 (OMIM Ref. No. 164870) in human breast cancer cells (Bosher et al., 1995).

Williamson et al. (1996) isolated an AP-2-related cDNA. The predicted protein differs from AP-2-alpha (OMIM Ref. No. 107580) and -beta (OMIM Ref. No. 601601) in the N-terminal activation domain, but is 75 to 85% conserved within the DNA-binding and dimerization domains. All 3 gene products (AP-2-alpha, -beta, and -gamma) bind the GCCNNNGGC motif. Williamson et al. (1996) also obtained

a genomic clone for AP-2-gamma (designated TFAP2C). They showed it to have a similar gene structure to TFAP2A and mapped it by fluorescence in situ hybridization to 20q13.2. A mouse genomic clone was used to map the mouse Tcfap2c locus to 2H3-4.

[18866] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18867] Bosher, J. M.; Williams, T.; Hurst, H. C. : The developmentally regulated transcription factor AP-2 is involved in c-erbB-2 overexpression in human mammary carcinoma. Proc. Nat. Acad. Sci. 92: 744-747, 1995. ; and

[18868] Williamson, J. A.; Bosher, J. M.; Skinner, A.; Sheer, D.; Williams, T.; Hurst, H. C. : Chromosomal mapping of the human and mouse homologues of two new members of the AP-2 family of tra.

[18869] Further studies establishing the function and utilities of TFAP2C are found in John Hopkins OMIM database record ID 601602, and in cited publications numbered 9340 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ20054 (Accession NM\_019049) is another VGAM379 host target gene. FLJ20054 BINDING SITE is HOST TARGET binding

site found in the 3` untranslated region of mRNA encoded by FLJ20054, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20054 BINDING SITE, designated SEQ ID:21130, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18870] Another function of VGAM379 is therefore inhibition of FLJ20054 (Accession NM\_019049). Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20054. HRD1 (Accession XM\_045498) is another VGAM379 host target gene. HRD1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HRD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HRD1 BINDING SITE, designated SEQ ID:34469, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18871] Another function of VGAM379 is therefore inhibition of

HRD1 (Accession XM\_045498). Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HRD1. p21(CDKN1A)-activated Kinase 7 (PAK7, Accession XM\_045653) is another VGAM379 host target gene. PAK7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAK7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAK7 BINDING SITE, designated SEQ ID:34510, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18872] Another function of VGAM379 is therefore inhibition of p21(CDKN1A)-activated Kinase 7 (PAK7, Accession XM\_045653). Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAK7. R3H Domain (binds single-stranded nucleic acids) Containing (R3HDM, Accession NM\_015361) is another VGAM379 host target gene. R3HDM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by R3HDM, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of R3HDM BINDING SITE, designated SEQ ID:17659, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18873] Another function of VGAM379 is therefore inhibition of R3H Domain (binds single-stranded nucleic acids) Containing (R3HDM, Accession NM\_015361). Accordingly, utilities of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with R3HDM. LOC146229 (Accession XM\_085387) is another VGAM379 host target gene. LOC146229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146229 BINDING SITE, designated SEQ ID:38114, to the nucleotide sequence of VGAM379 RNA, herein designated VGAM RNA, also designated SEQ ID:3090.

[18874] Another function of VGAM379 is therefore inhibition of LOC146229 (Accession XM\_085387). Accordingly, utilities

of VGAM379 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146229. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 380 (VGAM380) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18875] VGAM380 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM380 was detected is described hereinabove with reference to Figs. 1–8.

[18876] VGAM380 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Feline Immunodeficiency Virus. VGAM380 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18877] VGAM380 gene encodes a VGAM380 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM380 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM380 precursor RNA is designated SEQ ID:366, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:366 is located at position 8388 relative to the genome of Feline Immunodeficiency Virus.

[18878] VGAM380 precursor RNA folds onto itself, forming VGAM380 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18879] An enzyme complex designated DICER COMPLEX, `dices` the VGAM380 folded precursor RNA into VGAM380 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM380 RNA is designated SEQ ID:3091, and

is provided hereinbelow with reference to the sequence listing part.

[18880] VGAM380 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM380 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM380 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18881] VGAM380 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM380 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM380 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM380 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM380 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18882] The complementary binding of VGAM380 RNA, herein designated VGAM RNA, to host target binding sites on VGAM380 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM380 host target RNA into VGAM380 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18883] It is appreciated that VGAM380 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM380 host target genes. The mRNA of each one of this plurality of VGAM380 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM380 RNA, herein designated VGAM RNA, and which when bound by VGAM380 RNA causes inhibition of translation of respective one or more VGAM380 host target proteins.

[18884] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM380 gene, herein designated VGAM GENE, on one or more VGAM380 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18885] It is yet further appreciated that a function of VGAM380 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM380 include diagnosis, prevention and treatment of viral infection by Feline Immunodeficiency Virus. Specific functions, and accordingly utilities, of VGAM380 correlate with, and may be deduced from, the identity of the host target genes which VGAM380 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18886] Nucleotide sequences of the VGAM380 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM380 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM380 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM380 are further described hereinbelow with reference to Table 1.

[18887] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM380 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM380 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18888] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM380 gene, herein designated VGAM is inhibition of expression of VGAM380 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM380 correlate with, and may be deduced from, the identity of the target genes which VGAM380 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18889] Clathrin, Heavy Polypeptide (Hc) (CLTC, Accession NM\_004859) is a VGAM380 host target gene. CLTC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLTC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLTC BINDING SITE, designated SEQ ID:11268, to the nucleotide sequence of VGAM380 RNA, herein designated VGAM RNA, also designated SEQ ID:3091.

[18890] A function of VGAM380 is therefore inhibition of Clathrin, Heavy Polypeptide (Hc) (CLTC, Accession NM\_004859). Accordingly, utilities of VGAM380 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLTC. Sperm Associated Antigen 6 (SPAG6, Accession NM\_012443) is another VGAM380 host



target gene. SPAG6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPAG6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPAG6 BINDING SITE, designated SEQ ID:14818, to the nucleotide sequence of VGAM380 RNA, herein designated VGAM RNA, also designated SEQ ID:3091.

[18891] Another function of VGAM380 is therefore inhibition of Sperm Associated Antigen 6 (SPAG6, Accession NM\_012443). Accordingly, utilities of VGAM380 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPAG6. Zinc Finger Protein 144 (Mel-18) (ZNF144, Accession NM\_007144) is another VGAM380 host target gene. ZNF144 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF144, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF144 BINDING SITE, designated SEQ ID:13990, to the nucleotide sequence of VGAM380 RNA, herein designated VGAM RNA,

also designated SEQ ID:3091.

[18892] Another function of VGAM380 is therefore inhibition of Zinc Finger Protein 144 (Mel-18) (ZNF144, Accession NM\_007144), a gene which is a transcriptional repressor and may play a role in the control of cell proliferation. Accordingly, utilities of VGAM380 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF144. The function of ZNF144 has been established by previous studies. Ishida et al. (1993) isolated the human homolog of Mel18. The deduced human protein contains 344 amino acids with a RING-finger motif, a helix-loop-helix (HLH)-like structure, and a pro/ser-rich region. The MEL18 gene is conserved among vertebrates. Its mRNA is expressed at high levels in placenta, lung, and kidney, and at lower levels in liver, pancreas, and skeletal muscle

[18893] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18894] Tagawa, M.; Sakamoto, T.; Shigemoto, K.; Matsubara, H.; Tamura, Y.; Ito, T.; Nakamura, I.; Okitsu, A.; Imai, K.; Taniguchi, M. : Expression of novel DNA-binding protein with zinc finger structure in various tumor cells. J. Biol.

Chem. 265: 20021–20026, 1990. ; and

- [18895] Ishida, A.; Asano, H.; Hasegawa, M.; Koseki, H.; Ono, T.; Yoshida, M. C.; Taniguchi, M.; Kanno, M. : Cloning and chromosome mapping of the human Mel-18 gene which encodes a DNA-binding pr.
- [18896] Further studies establishing the function and utilities of ZNF144 are found in John Hopkins OMIM database record ID 600346, and in cited publications numbered 8284–828 and 8292 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC114971 (Accession XM\_054936) is another VGAM380 host target gene. LOC114971 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC114971, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC114971 BINDING SITE, designated SEQ ID:36204, to the nucleotide sequence of VGAM380 RNA, herein designated VGAM RNA, also designated SEQ ID:3091.
- [18897] Another function of VGAM380 is therefore inhibition of LOC114971 (Accession XM\_054936). Accordingly, utilities of VGAM380 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC114971. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 381 (VGAM381) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[18898] VGAM381 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM381 was detected is described hereinabove with reference to Figs. 1–8.

[18899] VGAM381 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Feline Immunodeficiency Virus. VGAM381 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[18900] VGAM381 gene encodes a VGAM381 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM381 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM381 precursor RNA is designated SEQ

ID:367, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:367 is located at position 8564 relative to the genome of Feline Immunodeficiency Virus.

[18901] VGAM381 precursor RNA folds onto itself, forming VGAM381 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[18902] An enzyme complex designated DICER COMPLEX, `dices` the VGAM381 folded precursor RNA into VGAM381 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM381 RNA is designated SEQ ID:3092, and is provided hereinbelow with reference to the sequence

listing part.

[18903] VGAM381 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM381 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM381 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[18904] VGAM381 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM381 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM381 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM381 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM381 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[18905] The complementary binding of VGAM381 RNA, herein designated VGAM RNA, to host target binding sites on VGAM381 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM381 host target RNA into VGAM381 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[18906] It is appreciated that VGAM381 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM381 host target genes. The mRNA of each one of this plurality of VGAM381 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM381 RNA, herein designated VGAM

RNA, and which when bound by VGAM381 RNA causes inhibition of translation of respective one or more VGAM381 host target proteins.

[18907] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM381 gene, herein designated VGAM GENE, on one or more VGAM381 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[18908] It is yet further appreciated that a function of VGAM381 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,



utilities of VGAM381 include diagnosis, prevention and treatment of viral infection by Feline Immunodeficiency Virus. Specific functions, and accordingly utilities, of VGAM381 correlate with, and may be deduced from, the identity of the host target genes which VGAM381 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[18909] Nucleotide sequences of the VGAM381 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM381 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM381 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM381 are further described hereinbelow with reference to Table 1.

[18910] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM381 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM381 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[18911] As mentioned hereinabove with reference to Fig. 1, a function of VGAM381 gene, herein designated VGAM is

inhibition of expression of VGAM381 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM381 correlate with, and may be deduced from, the identity of the target genes which VGAM381 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[18912] Angiotensinogen (serine (or cysteine) Proteinase Inhibitor, Clade A (alpha-1 antiproteinase, antitrypsin), Member 8) (AGT, Accession NM\_000029) is a VGAM381 host target gene. AGT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AGT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AGT BINDING SITE, designated SEQ ID:5469, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18913] A function of VGAM381 is therefore inhibition of Angiotensinogen (serine (or cysteine) Proteinase Inhibitor, Clade A (alpha-1 antiproteinase, antitrypsin), Member 8) (AGT, Accession NM\_000029). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AGT.

Asialoglycoprotein Receptor 2 (ASGR2, Accession NM\_080912) is another VGAM381 host target gene. ASGR2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ASGR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASGR2 BINDING SITE, designated SEQ ID:28129, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18914] Another function of VGAM381 is therefore inhibition of Asialoglycoprotein Receptor 2 (ASGR2, Accession NM\_080912). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASGR2. AXIN1 Up-regulated 1 (AXUD1, Accession NM\_033027) is another VGAM381 host target gene. AXUD1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AXUD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AXUD1 BINDING SITE, des-

ignated SEQ ID:26919, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18915] Another function of VGAM381 is therefore inhibition of AXIN1 Up-regulated 1 (AXUD1, Accession NM\_033027). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AXUD1. Chromosome 20 Open Reading Frame 1 (C20orf1, Accession NM\_012112) is another VGAM381 host target gene. C20orf1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf1 BINDING SITE, designated SEQ ID:14427, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18916] Another function of VGAM381 is therefore inhibition of Chromosome 20 Open Reading Frame 1 (C20orf1, Accession NM\_012112), a gene which is a nuclear proliferation-associated protein. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with C20orf1. The function of C20orf1 has been established by previous studies. Heidebrecht et al. (1997) determined that p100 is a nuclear proliferation-associated protein whose expression is restricted to cell cycle phases S, G2, and M. Using an mRNA differential display technique, Manda et al. (1999) isolated 2 novel cDNAs, SPON2 (OMIM Ref. No. 605918) and C20ORF1, which they designated differentially expressed in cancerous and noncancerous lung cells-1 (DIL1) and -2 (DIL2), respectively. The full-length C20ORF1 cDNA encodes a 747-amino acid protein with a putative ATP/GTP-binding site motif. RT-PCR analysis demonstrated strong expression of C20ORF1 in lung carcinoma cell lines. Northern blot analysis detected expression in fetal lung but not in adult lung. C20ORF1 expression was also found in adult placenta, skeletal muscle, thymus, testis, and small intestine and in fetal brain, liver, and kidney. By fluorescence in situ hybridization, Zhang et al. (1999) mapped the C20ORF1 gene to chromosome 20q11.2.

[18917] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18918] Manda, R.; Kohno, T.; Matsuno, Y.; Takenoshita, S.;

Kuwano, H.; Yokota, J. : Identification of genes (SPON2 and C20orf2) differentially expressed between cancerous and noncancerous lung cells by mRNA differential display. Genomics 61: 5–14, 1999. ; and

[18919] Heidebrecht, H. J.; Buck, F.; Steinmann, J.; Sprenger, R.; Wacker, H. H.; Parwaresch, R. : p100: a novel proliferation-associated nuclear protein specifically restricted to cell cycle p.

[18920] Further studies establishing the function and utilities of C20orf1 are found in John Hopkins OMIM database record ID 605917, and in cited publications numbered 97 and 6436–6437 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CD4 Antigen (p55) (CD4, Accession NM\_000616) is another VGAM381 host target gene. CD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD4 BINDING SITE, designated SEQ ID:6217, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18921] Another function of VGAM381 is therefore inhibition of CD4 Antigen (p55) (CD4, Accession NM\_000616), a gene which is T-cell surface glycoprotein and has role in cell-cell interactions and may act in signal transduction. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD4. The function of CD4 has been established by previous studies. In transgenic mice carrying the human CD4 gene, Buttini et al. (1998) found that human CD4 is expressed on microglia, the resident mononuclear phagocytes of brain. Normally there is no neuronal damage. Activation of brain microglia by peripheral immune challenges elicited neurodegeneration in human CD4 mice but not in nontransgenic controls. In postmortem brain tissues from AIDS patients with opportunistic infections, but without typical HIV encephalitis, human CD4 expression correlated with neurodegeneration. Buttini et al. (1998) concluded that human CD4 may function as an important mediator of indirect neuronal damage in infectious and immune-mediated diseases of the central nervous system (CNS). The important role of human CD4 expression on microglia/macrophages creates a pathogenetic link between the immune system and the CNS.

Animal model experiments lend further support to the function of CD4. In transgenic mice carrying the human CD4 gene, Buttini et al. (1998) found that human CD4 is expressed on microglia, the resident mononuclear phagocytes of brain. Normally there is no neuronal damage. Activation of brain microglia by peripheral immune challenges elicited neurodegeneration in human CD4 mice but not in nontransgenic controls. In postmortem brain tissues from AIDS patients with opportunistic infections, but without typical HIV encephalitis, human CD4 expression correlated with neurodegeneration. Buttini et al. (1998) concluded that human CD4 may function as an important mediator of indirect neuronal damage in infectious and immune-mediated diseases of the central nervous system (CNS). The important role of human CD4 expression on microglia/macrophages creates a pathogenetic link between the immune system and the CNS.

[18922] It is appreciated that the abovementioned animal model for CD4 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[18923] Full details of the abovementioned studies are described in the following publications, the disclosure of which are



hereby incorporated by reference:

- [18924] Buttini, M.; Westland, C. E.; Masliah, E.; Yafeh, A. M.; Wyss-Coray, T.; Mucke, L. : Novel role of human CD4 molecule identified in neurodegeneration. *Nature Med.* 4: 441–446, 1998. ; and
- [18925] Krummel, M. F.; Sjaastad, M. D.; Wulfing, C.; Davis, M. M. : Differential clustering of CD4 and CD3–zeta during T cell recognition. *Science* 289: 1349–1352, 2000.
- [18926] Further studies establishing the function and utilities of CD4 are found in John Hopkins OMIM database record ID 186940, and in cited publications numbered 10551–10558, 5690, 10559–10562, 5691, 6036, 10563–10566, 983 and 10960–10031 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Early Growth Response 1 (EGR1, Accession NM\_001964) is another VGAM381 host target gene. EGR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGR1 BINDING SITE, designated SEQ ID:7691, to the nucleotide sequence of VGAM381 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3092.

[18927] Another function of VGAM381 is therefore inhibition of Early Growth Response 1 (EGR1, Accession NM\_001964). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGR1. ELK1, Member of ETS Oncogene Family (ELK1, Accession NM\_005229) is another VGAM381 host target gene. ELK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ELK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELK1 BINDING SITE, designated SEQ ID:11728, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18928] Another function of VGAM381 is therefore inhibition of ELK1, Member of ETS Oncogene Family (ELK1, Accession NM\_005229), a gene which stimulates transcription. can form a ternary complex with the serum response factor and the ets and srf motifs of the fos serum response element. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical con-

ditions associated with ELK1. The function of ELK1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178.V-erb-a Erythroblastic Leukemia Viral Oncogene Homolog 4 (avian) (ERBB4, Accession NM\_005235) is another VGAM381 host target gene. ERBB4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ERBB4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ERBB4 BINDING SITE, designated SEQ ID:11744, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18929] Another function of VGAM381 is therefore inhibition of V-erb-a Erythroblastic Leukemia Viral Oncogene Homolog 4 (avian) (ERBB4, Accession NM\_005235), a gene which may function in growth/differentiation of normal and transformed cells. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ERBB4. The function of ERBB4 has been established by previous studies. The

HER4/ERBB4 gene is a member of the type I receptor tyrosine kinase subfamily that includes EGFR (OMIM Ref. No. 131550), ERBB2 (OMIM Ref. No. 164870), and ERBB3 (OMIM Ref. No. 190151). It encodes a receptor for NDF/heregulin (OMIM Ref. No. 142445). Neuregulins and their receptors, the ERBB protein tyrosine kinases, are essential for neuronal development. Huang et al. (2000) reported that ERBB4 is enriched in the postsynaptic density and associates with PSD95 (OMIM Ref. No. 602887). Heterologous expression of PSD95 enhanced NRG (OMIM Ref. No. 142445) activation of ERBB4 and MAP kinase (see OMIM Ref. No. 176948). Conversely, inhibiting expression of PSD95 in neurons attenuated NRG-mediated activation of MAP kinase. PSD95 formed a ternary complex with 2 molecules of ERBB4, suggesting that PSD95 facilitates ERBB4 dimerization. Finally, NRG suppressed induction of long-term potentiation in the hippocampal CA1 region without affecting basal synaptic transmission. Thus, NRG signaling may be synaptic and regulated by PSD95. Huang et al. (2000) concluded that a role of NRG signaling in the adult central nervous system may be modulation of synaptic plasticity. ERBB4 is a transmembrane receptor tyrosine kinase that regulates cell proliferation and differ-

entiation. After binding its ligand heregulin or activation of protein kinase C (see OMIM Ref. No. 176960) by TPA, the ERBB4 ectodomain is cleaved by a metalloprotease. Ni et al. (2001) reported a subsequent cleavage by gamma-secretase that releases the ERBB4 intracellular domain from the membrane and facilitates its translocation to the nucleus. Gamma-secretase cleavage was prevented by chemical inhibitors or a dominant-negative presenilin (OMIM Ref. No. 104311). Inhibition of gamma-secretase also prevented growth inhibition by heregulin. Ni et al. (2001) concluded that gamma-secretase cleavage of ERBB4 may represent another mechanism for receptor tyrosine kinase-mediated signaling. Using human cDNA probes in fluorescence in situ hybridization, Zimonjic et al. (1995) mapped the ERBB4 gene to 2q33.3-q34. The finding established that the ERBB4 gene, like the related EGFR, ERBB2, and ERBB3 genes, is located in close proximity to homeobox and collagen gene loci. Animal model experiments lend further support to the function of ERBB4. ErbB4  $-/-$  mouse embryos develop trigeminal ganglion and geniculate/cochleovestibular ganglia that are displaced toward each other and show axonal misprojections (Gassmann et al., 1995). Golding et al. (2000) found

that these morphologic changes correlate with aberrant migration of a subpopulation of hindbrain-derived cranial neural crest cells. The aberrant migration is also accompanied by an apparent downregulation of HoxB2 (OMIM Ref. No. 142967) gene expression.

[18930] It is appreciated that the abovementioned animal model for ERBB4 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[18931] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18932] Huang, Y. Z.; Won, S.; Ali, D. W.; Wang, Q.; Tanowitz, M.; Du, Q. S.; Pelkey, K. A.; Yang, D. J.; Xiong, W. C.; Salter, M. W.; Mei, L. : Regulation of neuregulin signaling by PSD-95 interacting with ErbB4 at CNS synapses. Neuron 26: 443-455, 2000. ; and

[18933] Golding, J. P.; Trainor, P.; Krumlauf, R.; Gassmann, M. : Defects in pathfinding by cranial neural crest cells in mice lacking the neuregulin receptor ErbB4. Nature Cell Biol. 2: 103-10.

[18934] Further studies establishing the function and utilities of ERBB4 are found in John Hopkins OMIM database record

ID 600543, and in cited publications numbered 7868–7869, 1157 and 11576 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Growth Factor Independent 1 (GFI1, Accession NM\_005263) is another VGAM381 host target gene. GFI1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GFI1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GFI1 BINDING SITE, designated SEQ ID:11769, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18935] Another function of VGAM381 is therefore inhibition of Growth Factor Independent 1 (GFI1, Accession NM\_005263). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GFI1. Guanine Nucleotide Binding Protein (G protein), Beta Polypeptide 1 (GNB1, Accession NM\_002074) is another VGAM381 host target gene. GNB1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GNB1, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GNB1 BINDING SITE, designated SEQ ID:7850, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18936] Another function of VGAM381 is therefore inhibition of Guanine Nucleotide Binding Protein (G protein), Beta Polypeptide 1 (GNB1, Accession NM\_002074). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNB1. Hepatic Leukemia Factor (HLF, Accession NM\_002126) is another VGAM381 host target gene. HLF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HLF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HLF BINDING SITE, designated SEQ ID:7903, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18937] Another function of VGAM381 is therefore inhibition of Hepatic Leukemia Factor (HLF, Accession NM\_002126). Accordingly, utilities of VGAM381 include diagnosis, pre-



vention and treatment of diseases and clinical conditions associated with HLF. High-mobility Group Nucleosome Binding Domain 1 (HMGN1, Accession NM\_004965) is another VGAM381 host target gene. HMGN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HMGN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HMGN1 BINDING SITE, designated SEQ ID:11412, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18938] Another function of VGAM381 is therefore inhibition of High-mobility Group Nucleosome Binding Domain 1 (HMGN1, Accession NM\_004965), a gene which binds to the inner side of the nucleosomal DNA and involves in transcriptional regulation. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HMGN1. The function of HMGN1 has been established by previous studies. See 163910. Chromosomal protein HMG14 and its close analog HMG17 (OMIM Ref. No. 163910) bind to the inner side of the nucleosomal DNA, potentially altering

the interaction between the DNA and the histone octamer. The 2 proteins may be involved in the process that maintains transcribable genes in a unique chromatin conformation. Their ubiquitous distribution, relative abundance, and high evolutionary conservation of the DNA-binding domain of the HMG-14 family of proteins, suggest that they may be involved in an important cellular function. The human HMG14 multigene family is 1 of the largest retropseudogene families known. However, Landsman et al. (1989) found only a single genomic clone selected with a cDNA, thus suggesting that the human genome contains few and perhaps only 1 functional gene. The gene was found to comprise 6 exons ranging in size from 30 to 839 bp, 2 of which code for the entire DNA binding site of the protein and have several features typical of 'housekeeping' genes. Using human-rodent somatic cell hybrids, Landsman et al. (1989) localized the HMG14 gene to human chromosome 21. They detected a RFLP useful for further analysis and mapping. Comparison with the human and chicken HMG17 genes showed that all contain 6 exons; all have exons of similar size; all have 5-prime regions highly enriched in GC residues; and all have features typical of housekeeping genes. Petersen et al. (1990) used a GT

dinucleotide repeat as a polymorphic marker in linkage analysis to demonstrate that the HMG14 locus is close to the ETS2 gene in band 21q22.3. By in situ hybridization, Pash et al. (1990) confirmed the assignment to 21q22.3. Furthermore, they analyzed the expression of the HMG14 gene in mouse embryos trisomic for chromosome 16 and found that trisomy 16 embryos had approximately 1.5 times more HMG14 mRNA and protein than their normal littermates. Pash et al. (1990) suggested that this nucleosomal binding protein may confer distinct properties to the chromatin structure of transcriptionally active genes and therefore may be a contributing factor in the development of Down syndrome. Since HMG14 is preferentially associated with transcriptionally active chromatin, Ding et al. (1994) assessed its effect on transcription by RNA polymerase II. They found that HMG14 enhanced transcription on chromatin templates but not on DNA templates. These findings suggested that the association of HMG14 with nucleosomes is part of the cellular process involved in the generation of transcriptionally active chromatin.

[18939] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

[18940] Ding, H.-F.; Rimsky, S.; Batson, S. C.; Bustin, M.; Hansen, U. : Stimulation of RNA polymerase II elongation by chromosomal protein HMG-14. Science 265: 796-799, 1994. ; and

[18941] Landsman, D.; McBride, O. W.; Soares, N.; Crippa, M. P.; Srikantha, T.; Bustin, M. : Chromosomal protein HMG-14: identification, characterization, and chromosome localization of a function.

[18942] Further studies establishing the function and utilities of HMGN1 are found in John Hopkins OMIM database record ID 163920, and in cited publications numbered 3019-3022 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Hormonally Upregulated Neu-associated Kinase (HUNK, Accession NM\_014586) is another VGAM381 host target gene. HUNK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HUNK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HUNK BINDING SITE, designated SEQ ID:15948, to the nucleotide sequence of VGAM381 RNA,

herein designated VGAM RNA, also designated SEQ ID:3092.

[18943] Another function of VGAM381 is therefore inhibition of Hormonally Upregulated Neu-associated Kinase (HUNK, Accession NM\_014586). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUNK. Myosin IC (MYO1C, Accession XM\_028385) is another VGAM381 host target gene. MYO1C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYO1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYO1C BINDING SITE, designated SEQ ID:30696, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18944] Another function of VGAM381 is therefore inhibition of Myosin IC (MYO1C, Accession XM\_028385), a gene which participates in adaptation in hair cells. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYO1C. The function of MYO1C has been established by

previous studies. MYO1C, also known as myosin I-beta and MYR2, was thought to mediate the slow component of adaptation by hair cells, the sensory cells of the inner ear. To test this hypothesis, Holt et al. (2002) mutated tyr61 of MYO1C to gly, conferring susceptibility to inhibition by N6-modified ADP analogs. They expressed the mutant MYO1C in utricular hair cells of transgenic mice, delivered an ADP analog through a whole-cell recording pipette, and found that the analog rapidly blocked adaptation to positive and negative deflections in transgenic cells but not in wildtype cells. The speed and specificity of inhibition suggested that MYO1C participates in adaptation in hair cells.

[18945] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18946] Crozet, F.; Amraoui, A. E.; Blanchard, S.; Lenoir, M.; Ripoll, C.; Vago, P.; Hamel, C.; Fizames, C.; Levi-Acobas, F.; Depetris, D.; Mattei, M.-G.; Weil, D.; Pujol, R.; Petit, C. : Cloning of the genes encoding two murine and human cochlear unconventional type I myosins. *Genomics* 40: 332-341, 1997. ; and

[18947] Holt, J. R.; Gillespie, S. K. H.; Provance, D. W., Jr.; Shah, K.;

Shokat, K. M.; Corey, D. P.; Mercer, J. A.; Gillespie, P. G. : A chemical-genetic strategy implicates myosin-1c in adap.

[18948] Further studies establishing the function and utilities of MYO1C are found in John Hopkins OMIM database record ID 606538, and in cited publications numbered 6515 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Paired Mesoderm Homeo Box 1 (PMX1, Accession NM\_022716) is another VGAM381 host target gene. PMX1 BINDING SITE1 and PMX1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PMX1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PMX1 BINDING SITE1 and PMX1 BINDING SITE2, designated SEQ ID:22914 and SEQ ID:13779 respectively, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18949] Another function of VGAM381 is therefore inhibition of Paired Mesoderm Homeo Box 1 (PMX1, Accession NM\_022716), a gene which acts as a transcriptional regulator of muscle creatine kinase. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PMX1. The function of PMX1 has been established by previous studies. Homeo box genes are expressed in specific temporal and spatial patterns and function as transcriptional regulators of developmental processes. The murine homeo box gene Pmx (paired mesoderm homeo box), previously called K-2 and mHox, is expressed in a mesodermally restricted pattern in embryos and most abundantly in cardiac, skeletal, and smooth muscle tissues in adults (Kern et al., 1994). Grueneberg et al. (1992) cloned the homologous human gene. By means of interspecific backcross analysis, Kern et al. (1994) determined that the Pmx gene is located on mouse chromosome 1, approximately 3.3 cM distal to the Gsh-4 homeo box locus. The gene contains at least 5 exons spanning a minimum of 60 kb of genomic DNA, making this the largest known murine homeo box gene. The homologous human gene may map to 1q inasmuch as this region is syntenic with the region of mouse chromosome 1 where Pmx is located. Norris et al. (2000) mapped the human PRRX1 gene to 1q23 by fluorescence in situ hybridization.

[18950] Full details of the abovementioned studies are described in the following publications, the disclosure of which are



hereby incorporated by reference:

- [18951] Grueneberg, D. A.; Natesan, S.; Alexandre, C.; Gilman, M. Z. : Human and Drosophila homeodomain proteins that enhance the DNA-binding activity of serum response factor. Science 257: 1089–1095, 1992. ; and
- [18952] Norris, R. A.; Scott, K. K.; Moore, C. S.; Stetten, G.; Brown, C. R.; Jabs, E. W.; Wulfsberg, E. A.; Yu, J.; Kern, M. J. : Human PRRX1 and PRRX2 genes: cloning, expression, genomic localiz.
- [18953] Further studies establishing the function and utilities of PMX1 are found in John Hopkins OMIM database record ID 167420, and in cited publications numbered 10955–10959 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily D, Member 1 (SMARCD1, Accession NM\_139071) is another VGAM381 host target gene. SMARCD1 BINDING SITE1 and SMARCD1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SMARCD1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of SMARCD1 BINDING SITE1 and SMARCD1 BINDING SITE2, designated SEQ ID:29142 and SEQ ID:9044 respectively, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18954] Another function of VGAM381 is therefore inhibition of SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily D, Member 1 (SMARCD1, Accession NM\_139071), a gene which is involved in chromatin assembly and remodeling. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMARCD1. The function of SMARCD1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152. Ubiquitin-conjugating Enzyme E2L 3 (UBE2L3, Accession NM\_003347) is another VGAM381 host target gene. UBE2L3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2L3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2L3 BINDING SITE, designated SEQ

ID:9359, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18955] Another function of VGAM381 is therefore inhibition of Ubiquitin-conjugating Enzyme E2L 3 (UBE2L3, Accession NM\_003347), a gene which catalyzes the covalent attachment of ubiquitin to other proteins. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2L3. The function of UBE2L3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM215. Wingless-type MMTV Integration Site Family, Member 1 (WNT1, Accession NM\_005430) is another VGAM381 host target gene. WNT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WNT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WNT1 BINDING SITE, designated SEQ ID:11896, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18956] Another function of VGAM381 is therefore inhibition of Wingless-type MMTV Integration Site Family, Member 1 (WNT1, Accession NM\_005430), a gene which may have a role in development of the central nervous system. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WNT1. The function of WNT1 has been established by previous studies. Int oncogenes, including Int1, were first identified as targets for insertional activation by the mouse mammary tumor virus (MMTV) in mammary carcinomas. Int2 (see OMIM Ref. No. 164950) and Int3 (see OMIM Ref. No. 164951) are fundamentally unrelated genes; the similarity in nomenclature is based on the criterion of being a target for MMTV insertion mutation. Nusse et al. (1991) proposed that the INT1 gene be termed WNT1 (pronounced 'wint 1'), because it was both an INT gene and a homolog of the *Drosophila* 'wingless' gene. The WNTs are a family of secreted glycoproteins that have been shown to be involved in a variety of developmental processes in many organisms. The prototype of the family is the *Drosophila* protein 'wingless' which acts as a segment polarity gene during embryogenesis and later participates in pattern formation of other body parts.

Gavin et al. (1990) isolated 7 murine Wnt family members; Wolda and Moon (1992) isolated 7 *Xenopus* Wnt family members. McMahon (1992) discussed the Wnt family of developmental regulators, with particular reference to mouse mammary gland and the development of mouse mammary tumors. INT1 has a highly specific (both temporal and spatial) pattern of expression in fetal brain and spinal cord from 9- to 10-day-old mouse embryos but has been demonstrated to be expressed in only 1 adult tissue, postmyotic spermatids. The *Drosophila* homolog of INT1 is 'wingless,' a segment-polarity gene. Indirect evidence that INT1 is secreted and that the product of 'wingless' is a diffusible gene product suggests that these proteins are secreted growth factors. By analyzing human genome draft sequence, Kirikoshi et al. (2001) determined that WNT1 is encoded by 4 exons and is clustered with WNT10B (OMIM Ref. No. 601906) in a head-to-head manner within an interval of less than 7 kb. They discussed possibilities for the origin of WNT gene clusters through duplication of an ancestral WNT gene cluster. Animal model experiments lend further support to the function of WNT1. Tsukamoto et al. (1988) generated transgenic mice ectopically expressing Wnt1 RNA at high levels in mam-

mary and salivary glands of male and female mice and in male reproductive organs. The mammary glands of males and virgin females were grossly hyperplastic compared with those of nontransgenic littermates. Tsukamoto et al. (1988) observed mammary and (less frequently) salivary adenocarcinomas in these animals at rates indicating that transcriptional activation of Wnt1 and associated hyperplasia are initiating events in multistep carcinogenesis. Thomas and Capecchi (1990) explored the function of int1 in the mouse by disrupting one of the 2 int1 alleles in mouse embryo-derived stem cells using positive-negative selection. This cell line was then used to generate a chimeric mouse that transmitted the mutant allele to its progeny. Mice heterozygous for the null mutation were normal and fertile, whereas mice homozygous for the mutation exhibited a range of phenotypes from death before birth to survival with severe ataxia. Examination of homozygous mice at several stages of embryogenesis showed severe abnormalities in the development of the mesencephalon and metencephalon, indicating a prominent role for the int1 protein in the induction of the mesencephalon and cerebellum.

[18957] It is appreciated that the abovementioned animal model

for WNT1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[18958] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18959] Kirikoshi, H.; Sekihara, H.; Katoh, M. : WNT10A and WNT6, clustered in human chromosome 2q35 region with head-to-tail manner, are strongly coexpressed in SW480 cells. Biochem. Biophys. Res. Commun. 283: 798–805, 2001. ; and

[18960] Wolda, S. L.; Moon, R. T. : Cloning and developmental expression in *Xenopus laevis* of seven additional members of the Wnt family. Oncogene 7: 1941–1947, 1992.

[18961] Further studies establishing the function and utilities of WNT1 are found in John Hopkins OMIM database record ID 164820, and in cited publications numbered 12746–12753, 882, 1724, 3475–172 and 3972 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zic Family Member 1 (odd-paired homolog, *Drosophila*) (ZIC1, Accession NM\_003412) is another VGAM381 host target gene. ZIC1 BINDING SITE is HOST TARGET binding site found in the

5' untranslated region of mRNA encoded by ZIC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZIC1 BINDING SITE, designated SEQ ID:9447, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18962] Another function of VGAM381 is therefore inhibition of Zic Family Member 1 (odd-paired homolog, *Drosophila*) (ZIC1, Accession NM\_003412), a gene which may play a role in cerebellar development. Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZIC1. The function of ZIC1 has been established by previous studies. mouse cerebellum and is highly homologous to the *Drosophila* pair-rule gene Opa. To clarify the mechanism for the development of the human cerebellum and the possible involvement of ZIC in human nervous system diseases, Yokota et al. (1996) isolated human ZIC cDNA and examined its expression by using monoclonal antibody against recombinant ZIC protein. The nucleotide sequence of human ZIC cDNA is 85% homologous to that the mouse zic gene. Its putative amino acid sequence is highly conserved



(more than 99%) except for substitution of only 2 amino acid residues. By fluorescence in situ hybridization, Yokota et al. (1996) mapped the human ZIC gene to 3q24. The human ZIC protein was immunohistochemically detected in the nuclei of the cerebellar granule cell lineage from the progenitor cells of the external germinal layer to the postmigrated cells of the internal granular layer. Furthermore, ZIC protein was detected in medulloblastoma (26 of 29 cases), whereas none of 70 other tumors examined, including primitive neuroectodermal tumors, expressed this protein. These findings suggested that ZIC is a potential biomarker for medulloblastoma as well as the human cerebellar granule cell lineage.

[18963] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[18964] Aruga, J.; Yokota, N.; Hashimoto, M.; Furuichi, T.; Fukuda, M.; Mikoshiba, K. : A novel zinc finger protein, Zic, is involved in neurogenesis, especially in the cell lineage of cerebellar granule cells. *J. Neurochem.* 63: 1880–1890, 1994. ; and

[18965] Yokota, N.; Aruga, J.; Takai, S.; Yamada, K.; Hamazaki, M.; Iwase, T.; Sugimura, H.; Mikoshiba, K. : Predominant ex–

pression of human Zic in cerebellar granule cell lineage and medulloblasto.

[18966] Further studies establishing the function and utilities of ZIC1 are found in John Hopkins OMIM database record ID 600470, and in cited publications numbered 7734–7736 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZp547G183 (Accession NM\_018705) is another VGAM381 host target gene. DKFZp547G183 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp547G183, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547G183 BINDING SITE, designated SEQ ID:20788, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18967] Another function of VGAM381 is therefore inhibition of DKFZp547G183 (Accession NM\_018705). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547G183. FLJ12783 (Accession NM\_031426) is another VGAM381 host target gene. FLJ12783 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12783, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12783 BINDING SITE, designated SEQ ID:25416, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18968] Another function of VGAM381 is therefore inhibition of FLJ12783 (Accession NM\_031426). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12783. FLJ13102 (Accession NM\_024887) is another VGAM381 host target gene. FLJ13102 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13102, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13102 BINDING SITE, designated SEQ ID:24342, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18969] Another function of VGAM381 is therefore inhibition of

FLJ13102 (Accession NM\_024887). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13102. FLJ13848 (Accession NM\_024771) is another VGAM381 host target gene. FLJ13848 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13848 BINDING SITE, designated SEQ ID:24133, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18970] Another function of VGAM381 is therefore inhibition of FLJ13848 (Accession NM\_024771). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13848. FLJ13993 (Accession XM\_017638) is another VGAM381 host target gene. FLJ13993 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13993, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ13993 BINDING SITE, designated SEQ ID:30328, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18971] Another function of VGAM381 is therefore inhibition of FLJ13993 (Accession XM\_017638). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13993. FLJ22944 (Accession NM\_025145) is another VGAM381 host target gene. FLJ22944 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22944, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22944 BINDING SITE, designated SEQ ID:24785, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18972] Another function of VGAM381 is therefore inhibition of FLJ22944 (Accession NM\_025145). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22944. FLJ32334 (Accession NM\_144565) is another VGAM381

host target gene. FLJ32334 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ32334, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32334 BINDING SITE, designated SEQ ID:29370, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18973] Another function of VGAM381 is therefore inhibition of FLJ32334 (Accession NM\_144565). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32334. GTP Binding Protein 2 (GTPBP2, Accession NM\_019096) is another VGAM381 host target gene. GTPBP2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GTPBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GTPBP2 BINDING SITE, designated SEQ ID:21172, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18974] Another function of VGAM381 is therefore inhibition of GTP Binding Protein 2 (GTPBP2, Accession NM\_019096). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GTPBP2. HSPC065 (Accession NM\_014157) is another VGAM381 host target gene. HSPC065 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HSPC065, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC065 BINDING SITE, designated SEQ ID:15449, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18975] Another function of VGAM381 is therefore inhibition of HSPC065 (Accession NM\_014157). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC065. IMPACT (Accession NM\_018439) is another VGAM381 host target gene. IMPACT BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by IMPACT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BIND-

ING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IMPACT BINDING SITE, designated SEQ ID:20502, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18976] Another function of VGAM381 is therefore inhibition of IMPACT (Accession NM\_018439). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IMPACT. KIAA0258 (Accession NM\_014785) is another VGAM381 host target gene. KIAA0258 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0258, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0258 BINDING SITE, designated SEQ ID:16643, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18977] Another function of VGAM381 is therefore inhibition of KIAA0258 (Accession NM\_014785). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



KIAA0258. KIAA0853 (Accession NM\_015070) is another VGAM381 host target gene. KIAA0853 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0853, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0853 BINDING SITE, designated SEQ ID:17436, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18978] Another function of VGAM381 is therefore inhibition of KIAA0853 (Accession NM\_015070). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0853. KIAA1111 (Accession XM\_171233) is another VGAM381 host target gene. KIAA1111 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1111, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1111 BINDING SITE, designated SEQ ID:46019, to the nucleotide sequence of VGAM381 RNA, herein designated

VGAM RNA, also designated SEQ ID:3092.

[18979] Another function of VGAM381 is therefore inhibition of KIAA1111 (Accession XM\_171233). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1111. KIAA1854 (Accession XM\_049884) is another VGAM381 host target gene. KIAA1854 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1854, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1854 BINDING SITE, designated SEQ ID:35521, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18980] Another function of VGAM381 is therefore inhibition of KIAA1854 (Accession XM\_049884). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1854. KIAA1887 (Accession XM\_084801) is another VGAM381 host target gene. KIAA1887 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1887, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1887 BINDING SITE, designated SEQ ID:37714, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18981] Another function of VGAM381 is therefore inhibition of KIAA1887 (Accession XM\_084801). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1887. MGC17330 (Accession NM\_052880) is another VGAM381 host target gene. MGC17330 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC17330, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC17330 BINDING SITE, designated SEQ ID:27460, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18982] Another function of VGAM381 is therefore inhibition of MGC17330 (Accession NM\_052880). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with MGC17330. MGC2541 (Accession NM\_080670) is another VGAM381 host target gene. MGC2541 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2541, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2541 BINDING SITE, designated SEQ ID:27965, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18983] Another function of VGAM381 is therefore inhibition of MGC2541 (Accession NM\_080670). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2541. P66 (Accession NM\_020699) is another VGAM381 host target gene. P66 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P66, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P66 BINDING SITE, designated SEQ ID:21842, to the nucleotide sequence of

VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18984] Another function of VGAM381 is therefore inhibition of P66 (Accession NM\_020699). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P66. Serine/threonine Kinase 38 Like (STK38L, Accession XM\_044823) is another VGAM381 host target gene. STK38L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STK38L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STK38L BINDING SITE, designated SEQ ID:34288, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18985] Another function of VGAM381 is therefore inhibition of Serine/threonine Kinase 38 Like (STK38L, Accession XM\_044823). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STK38L. LOC112868 (Accession XM\_053402) is another VGAM381 host target

gene. LOC112868 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC112868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112868 BINDING SITE, designated SEQ ID:36076, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18986] Another function of VGAM381 is therefore inhibition of LOC112868 (Accession XM\_053402). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112868. LOC126528 (Accession XM\_059052) is another VGAM381 host target gene. LOC126528 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC126528, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126528 BINDING SITE, designated SEQ ID:36845, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18987] Another function of VGAM381 is therefore inhibition of LOC126528 (Accession XM\_059052). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126528. LOC126661 (Accession XM\_059061) is another VGAM381 host target gene. LOC126661 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC126661, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126661 BINDING SITE, designated SEQ ID:36849, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18988] Another function of VGAM381 is therefore inhibition of LOC126661 (Accession XM\_059061). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126661. LOC127534 (Accession XM\_060532) is another VGAM381 host target gene. LOC127534 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC127534, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127534 BINDING SITE, designated SEQ ID:37166, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18989] Another function of VGAM381 is therefore inhibition of LOC127534 (Accession XM\_060532). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127534. LOC144100 (Accession XM\_084732) is another VGAM381 host target gene. LOC144100 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144100, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144100 BINDING SITE, designated SEQ ID:37677, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18990] Another function of VGAM381 is therefore inhibition of LOC144100 (Accession XM\_084732). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC144100. LOC144289 (Accession XM\_096565) is another VGAM381 host target gene. LOC144289 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144289, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144289 BINDING SITE, designated SEQ ID:40397, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18991] Another function of VGAM381 is therefore inhibition of LOC144289 (Accession XM\_096565). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144289. LOC145468 (Accession XM\_057874) is another VGAM381 host target gene. LOC145468 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145468, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145468 BINDING SITE, designated SEQ ID:36547, to the nucleotide sequence of VGAM381 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3092.

[18992] Another function of VGAM381 is therefore inhibition of LOC145468 (Accession XM\_057874). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145468. LOC145854 (Accession XM\_085259) is another VGAM381 host target gene. LOC145854 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145854, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145854 BINDING SITE, designated SEQ ID:38005, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18993] Another function of VGAM381 is therefore inhibition of LOC145854 (Accession XM\_085259). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145854. LOC150150 (Accession XM\_097820) is another VGAM381 host target gene. LOC150150 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150150, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150150 BINDING SITE, designated SEQ ID:41135, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18994] Another function of VGAM381 is therefore inhibition of LOC150150 (Accession XM\_097820). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150150. LOC150155 (Accession XM\_047977) is another VGAM381 host target gene. LOC150155 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150155 BINDING SITE, designated SEQ ID:35088, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18995] Another function of VGAM381 is therefore inhibition of LOC150155 (Accession XM\_047977). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC150155. LOC150299 (Accession XM\_097869) is another VGAM381 host target gene. LOC150299 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150299, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150299 BINDING SITE, designated SEQ ID:41180, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18996] Another function of VGAM381 is therefore inhibition of LOC150299 (Accession XM\_097869). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150299. LOC158956 (Accession XM\_039450) is another VGAM381 host target gene. LOC158956 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158956, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158956 BINDING SITE, designated SEQ ID:33096, to

the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18997] Another function of VGAM381 is therefore inhibition of LOC158956 (Accession XM\_039450). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158956. LOC163412 (Accession XM\_088868) is another VGAM381 host target gene. LOC163412 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC163412, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163412 BINDING SITE, designated SEQ ID:39949, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18998] Another function of VGAM381 is therefore inhibition of LOC163412 (Accession XM\_088868). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163412. LOC256222 (Accession XM\_173177) is another VGAM381 host target gene. LOC256222 BINDING SITE is HOST TARGET binding site found in the 5` un-

translated region of mRNA encoded by LOC256222, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256222 BINDING SITE, designated SEQ ID:46425, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[18999] Another function of VGAM381 is therefore inhibition of LOC256222 (Accession XM\_173177). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256222. LOC51170 (Accession NM\_016245) is another VGAM381 host target gene. LOC51170 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51170 BINDING SITE, designated SEQ ID:18362, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[19000] Another function of VGAM381 is therefore inhibition of LOC51170 (Accession NM\_016245). Accordingly, utilities

of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51170. LOC90288 (Accession XM\_030669) is another VGAM381 host target gene. LOC90288 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90288, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90288 BINDING SITE, designated SEQ ID:31114, to the nucleotide sequence of VGAM381 RNA, herein designated VGAM RNA, also designated SEQ ID:3092.

[19001] Another function of VGAM381 is therefore inhibition of LOC90288 (Accession XM\_030669). Accordingly, utilities of VGAM381 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90288. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 382 (VGAM382) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19002] VGAM382 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM382 was detected is described hereinabove with reference to Figs. 1–8.

[19003] VGAM382 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis A Virus. VGAM382 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19004] VGAM382 gene encodes a VGAM382 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM382 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM382 precursor RNA is designated SEQ ID:368, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:368 is located at position 4814 relative to the genome of Hepatitis A Virus.

[19005] VGAM382 precursor RNA folds onto itself, forming VGAM382 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this



`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19006] An enzyme complex designated DICER COMPLEX, `dices` the VGAM382 folded precursor RNA into VGAM382 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM382 RNA is designated SEQ ID:3093, and is provided hereinbelow with reference to the sequence listing part.

[19007] VGAM382 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM382 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM382 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[19008] VGAM382 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM382 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM382 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM382 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM382 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19009] The complementary binding of VGAM382 RNA, herein designated VGAM RNA, to host target binding sites on VGAM382 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM382 host target RNA into VGAM382 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19010] It is appreciated that VGAM382 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM382 host target genes. The mRNA of each one of this plurality of VGAM382 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM382 RNA, herein designated VGAM RNA, and which when bound by VGAM382 RNA causes inhibition of translation of respective one or more VGAM382 host target proteins.

[19011] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM382 gene, herein designated VGAM GENE, on one or more VGAM382 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19012] It is yet further appreciated that a function of VGAM382 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM382 include diagnosis, prevention and treatment of viral infection by Hepatitis A Virus. Specific functions, and accordingly utilities, of VGAM382 correlate with, and may be deduced from, the identity of the host target genes which VGAM382 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19013] Nucleotide sequences of the VGAM382 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM382 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM382 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM382 are further  
described hereinbelow with reference to Table 1.

[19014] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM382 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM382 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[19015] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM382 gene, herein designated VGAM is  
inhibition of expression of VGAM382 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM382 correlate with, and may be deduced  
from, the identity of the target genes which VGAM382  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[19016] Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC,  
Accession NM\_080923) is a VGAM382 host target gene.

PTPRC BINDING SITE1 through PTPRC BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PTPRC, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPRC BINDING SITE1 through PTPRC BINDING SITE3, designated SEQ ID:28150, SEQ ID:8719 and SEQ ID:28145 respectively, to the nucleotide sequence of VGAM382 RNA, herein designated VGAM RNA, also designated SEQ ID:3093.

[19017] A function of VGAM382 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_080923). Accordingly, utilities of VGAM382 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRC. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 383 (VGAM383) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19018] VGAM383 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM383 was detected is described hereinabove with reference to Figs. 1–8.

[19019] VGAM383 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis A Virus.

VGAM383 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19020] VGAM383 gene encodes a VGAM383 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM383 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM383 precursor RNA is designated SEQ ID:369, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:369 is located at position 6678 relative to the genome of Hepatitis A Virus.

[19021] VGAM383 precursor RNA folds onto itself, forming VGAM383 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19022] An enzyme complex designated DICER COMPLEX, `dices` the VGAM383 folded precursor RNA into VGAM383 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM383 RNA is designated SEQ ID:3094, and is provided hereinbelow with reference to the sequence listing part.

[19023] VGAM383 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM383 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM383 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19024] VGAM383 RNA, herein designated VGAM RNA, binds com-



plementarily to one or more host target binding sites located in untranslated regions of VGAM383 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM383 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM383 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM383 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[19025] The complementary binding of VGAM383 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM383 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM383 host target RNA into VGAM383 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19026] It is appreciated that VGAM383 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM383 host target genes. The mRNA of each one of this plurality of VGAM383 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM383 RNA, herein designated VGAM RNA, and which when bound by VGAM383 RNA causes inhibition of translation of respective one or more VGAM383 host target proteins.

[19027] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM383 gene, herein designated VGAM GENE, on one or more VGAM383 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19028] It is yet further appreciated that a function of VGAM383 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of viral infection by Hepatitis A Virus. Specific functions, and accordingly utilities, of VGAM383 correlate with, and may be deduced from, the identity of the host target genes which VGAM383 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19029] Nucleotide sequences of the VGAM383 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM383 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM383 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM383 are further described hereinbelow with reference to Table 1.

[19030] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM383 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM383 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19031] As mentioned hereinabove with reference to Fig. 1, a function of VGAM383 gene, herein designated VGAM is inhibition of expression of VGAM383 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM383 correlate with, and may be deduced from, the identity of the target genes which VGAM383 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19032] Kinesin Family Member 5C (KIF5C, Accession NM\_004522) is a VGAM383 host target gene. KIF5C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIF5C, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIF5C BINDING SITE, designated SEQ ID:10859, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19033] A function of VGAM383 is therefore inhibition of Kinesin Family Member 5C (KIF5C, Accession NM\_004522). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIF5C. Membrane Cofactor Protein (CD46, trophoblast-lymphocyte cross-reactive antigen) (MCP, Accession NM\_002389) is another VGAM383 host target gene. MCP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MCP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MCP BINDING SITE, designated SEQ ID:8204, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19034] Another function of VGAM383 is therefore inhibition of Membrane Cofactor Protein (CD46, trophoblast-lympho-

cyte cross-reactive antigen) (MCP, Accession NM\_002389), a gene which may be involved in the regulation of complement activation. Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MCP. The function of MCP has been established by previous studies. MCP, a C3B/C4B-binding molecule of the complement system with cofactor activity for the I-dependent cleavage of C3B and C4B, is widely distributed in white blood cells, platelets, epithelial cells, and fibroblasts. Lublin et al. (1988) purified MCP from a human T-cell line and determined the sequence of the N-terminal 24 amino acids. An oligonucleotide probe was used to identify a clone from a human monocyte cDNA library. The deduced full-length MCP consists of a 34-amino acid signal peptide and a 350-amino acid mature protein. The protein has, beginning at the N terminus, 4 cysteine-rich repeating units (short consensus repeats, or SCRs) of about 60 amino acids each that match the consensus sequence found in a multigene family of complement regulatory proteins: CR1 (OMIM Ref. No. 120620), CR2 (OMIM Ref. No. 120650), C4BP (OMIM Ref. No. 120830), FH (OMIM Ref. No. 134370), and DAF (OMIM Ref. No. 125240). Immediately

C-terminal of the SCRs is a serine/threonine/proline (STP)-rich region, a likely area for extensive O-glycosylation. MCP also has a transmembrane domain, a basic amino acid anchor, and a cytoplasmic tail. Purcell et al. (1991) and Post et al. (1991) identified 4 and 6 isoforms of MCP, respectively. Post et al. (1991) demonstrated that the 6 isoforms vary in having 1 of 2 cytoplasmic tails and by having either all 3 STP regions (termed A, B, and C) or only STP-BC or STP-C. They showed that the STP-C isoforms are expressed as 45- to 55-kD proteins, the STP-BC isoforms are expressed as 55- to 65-kD proteins, and the STP-ABC isoforms are expressed as 65- to 75-kD proteins. The 65- to 75-kD variants were not expressed on peripheral blood cells or cell lines. Post et al. (1991) concluded that the presence of the B region of the STP area, which is richer in O-linked sugars, determines the expression of the 2 broad protein species. They also noted that up to 4 different forms of MCP are expressed on a single cell. Lublin et al. (1988) localized MCP to 1q31-q41 by Southern analysis of human-rodent somatic cell hybrid DNA and by in situ hybridization. This was the sixth member of this multigene family that had been assigned to this region of the genome. Bora et al. (1989)

demonstrated that the MCP gene is on the same 1,250-kb NotI fragment that contains CR1, CR2, DAF, and C4BP and maps within 100 kb of the 3-prime end of the CR1 gene. The order of the genes appears to be that just indicated, with MCP preceding the other 4 genes. Animal model experiments lend further support to the function of MCP. Marie et al. (2002) studied mice transgenic for human CD46 isoforms differing in their STP regions and in the length of their cytoplasmic domains. Mice expressing the 16-amino acid cytoplasmic tail variant, dubbed CD46-1, inhibited the T cell-mediated contact hypersensitivity reaction, whereas those expression the 23-residue cytoplasmic tail variant, termed CD46-2, increased it. CD46 stimulation or costimulation resulted in decreased cytotoxic activity and IL2 production, but increased proliferation and IL10 production, in CD46-1 transgenic mice. The effects were reversed in CD46-2 mice.

[19035] It is appreciated that the abovementioned animal model for MCP is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[19036] Full details of the abovementioned studies are described in the following publications, the disclosure of which are



hereby incorporated by reference:

- [19037] Lublin, D. M.; Liszewski, M. K.; Post, T. W.; Arce, M. A.; LeBeau, M. M.; Rebentisch, M. B.; Lemons, R. S.; Seya, T.; Atkinson, J. P. : Molecular cloning and chromosomal localization of human complement membrane cofactor protein (MCP): evidence for inclusion in the multigene family of complement-regulatory proteins. J. Exp. Med. 168: 181-194, 1988. ; and
- [19038] Post, T. W.; Liszewski, M. K.; Adams, E. M.; Tedja, I.; Miller, E. A.; Atkinson, J. P. : Membrane cofactor protein of the complement system: alternative splicing of serine/threonine/prol.
- [19039] Further studies establishing the function and utilities of MCP are found in John Hopkins OMIM database record ID 120920, and in cited publications numbered 347-356 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Src-like-adaptor (SLA, Accession NM\_006748) is another VGAM383 host target gene. SLA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of SLA BINDING SITE, designated SEQ ID:13596, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19040] Another function of VGAM383 is therefore inhibition of Src-like-adaptor (SLA, Accession NM\_006748), a gene which is a negative regulator of T-cell receptor signaling. Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLA. The function of SLA has been established by previous studies. Pandey et al. (1995) isolated a mouse cDNA using the 2-hybrid system to screen for molecules that interact with the cytoplasmic domain of Eck, a mouse receptor protein kinase (OMIM Ref. No. 176946). The predicted 281-amino acid protein has both SH3 and SH2 adaptor motifs similar to those in the Src family of nonreceptor tyrosine kinases but had no catalytic domain. The protein was named Slap (Src-like adaptor protein) by the authors. Recombinant Slap was shown to bind to activated Eck receptor tyrosine kinase. Angrist et al. (1995) cloned a cDNA for the putative human homolog of the gene, symbolized SLA. The predicted protein has 87% overall identity to the mouse sequence. Sosinowski et al. (2000) showed that SLA is a negative regula-

tor of T-cell receptor signaling. Holland et al. (2001) demonstrated that SLA and SLA2 (OMIM Ref. No. 606577) are both involved in downregulating T and B cell-mediated responses.

[19041] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19042] Angrist, M.; Wells, D. E.; Chakravarti, A.; Pandey, A. : Chromosomal localization of the mouse Src-like adapter protein (Slap) gene and its putative human homolog SLA. Genomics 30: 623–625, 1995. ; and

[19043] Sosinowski, T.; Pandey, A.; Dixit, V. M.; Weiss, A. : Src-like adaptor protein (SLAP) is a negative regulator of T cell receptor signaling. J. Exp. Med. 191: 463–474, 2000.

[19044] Further studies establishing the function and utilities of SLA are found in John Hopkins OMIM database record ID 601099, and in cited publications numbered 9491–949 and 9826 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SORCS1 (Accession NM\_052918) is another VGAM383 host target gene. SORCS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SORCS1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SORCS1 BINDING SITE, designated SEQ ID:27481, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19045] Another function of VGAM383 is therefore inhibition of SORCS1 (Accession NM\_052918). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORCS1. Tumor Necrosis Factor, Alpha-induced Protein 1 (endothelial) (TNFAIP1, Accession NM\_021137) is another VGAM383 host target gene. TNFAIP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFAIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFAIP1 BINDING SITE, designated SEQ ID:22111, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19046] Another function of VGAM383 is therefore inhibition of Tumor Necrosis Factor, Alpha-induced Protein 1

(endothelial) (TNFAIP1, Accession NM\_021137). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFAIP1. Aminoadipate-semialdehyde Dehydrogenase-phosphopantetheinyl Transferase (AASDHPPT, Accession NM\_015423) is another VGAM383 host target gene. AASDHPPT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AASDHPPT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AASDHPPT BINDING SITE, designated SEQ ID:17724, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19047] Another function of VGAM383 is therefore inhibition of Aminoadipate-semialdehyde Dehydrogenase-phosphopantetheinyl Transferase (AASDHPPT, Accession NM\_015423). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AASDHPPT. DDM36 (Accession NM\_020962) is another VGAM383 host target gene. DDM36 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by DDM36, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDM36 BINDING SITE, designated SEQ ID:21954, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19048] Another function of VGAM383 is therefore inhibition of DDM36 (Accession NM\_020962). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDM36. FLJ10853 (Accession NM\_018246) is another VGAM383 host target gene. FLJ10853 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10853, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10853 BINDING SITE, designated SEQ ID:20213, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19049] Another function of VGAM383 is therefore inhibition of

FLJ10853 (Accession NM\_018246). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10853. FLJ14146 (Accession NM\_024709) is another VGAM383 host target gene. FLJ14146 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14146, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14146 BINDING SITE, designated SEQ ID:24035, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19050] Another function of VGAM383 is therefore inhibition of FLJ14146 (Accession NM\_024709). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14146. KIAA0534 (Accession XM\_049349) is another VGAM383 host target gene. KIAA0534 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0534, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0534 BINDING SITE, designated SEQ ID:35380, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19051] Another function of VGAM383 is therefore inhibition of KIAA0534 (Accession XM\_049349). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0534. KIAA1918 (Accession XM\_054951) is another VGAM383 host target gene. KIAA1918 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1918, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1918 BINDING SITE, designated SEQ ID:36213, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19052] Another function of VGAM383 is therefore inhibition of KIAA1918 (Accession XM\_054951). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1918. Myosin 5C (MYO5C, Accession NM\_018728) is



another VGAM383 host target gene. MYO5C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYO5C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYO5C BINDING SITE, designated SEQ ID:20818, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19053] Another function of VGAM383 is therefore inhibition of Myosin 5C (MYO5C, Accession NM\_018728). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYO5C. Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4G (SEMA4G, Accession XM\_170638) is another VGAM383 host target gene. SEMA4G BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SEMA4G, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA4G BINDING SITE, designated SEQ ID:45409, to the

nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19054] Another function of VGAM383 is therefore inhibition of Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4G (SEMA4G, Accession XM\_170638). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA4G. LOC152580 (Accession XM\_098240) is another VGAM383 host target gene. LOC152580 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152580, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152580 BINDING SITE, designated SEQ ID:41522, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19055] Another function of VGAM383 is therefore inhibition of LOC152580 (Accession XM\_098240). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC152580. LOC91660 (Accession XM\_039902) is another VGAM383 host target gene. LOC91660 BINDING SITE1 and LOC91660 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC91660, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91660 BINDING SITE1 and LOC91660 BINDING SITE2, designated SEQ ID:33207 and SEQ ID:33210 respectively, to the nucleotide sequence of VGAM383 RNA, herein designated VGAM RNA, also designated SEQ ID:3094.

[19056] Another function of VGAM383 is therefore inhibition of LOC91660 (Accession XM\_039902). Accordingly, utilities of VGAM383 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91660. G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_014776) is another VGAM384 host target gene. GIT2 BINDING SITE1 through GIT2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GIT2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of GIT2 BINDING SITE1 through GIT2 BINDING SITE3, designated SEQ ID:16601, SEQ ID:27683 and SEQ ID:27696 respectively, to the nucleotide sequence of VGAM384 RNA, herein designated VGAM RNA, also designated SEQ ID:3095.

[19057] Another function of VGAM384 is therefore inhibition of G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_014776). Accordingly, utilities of VGAM384 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GIT2. LOC154282 (Accession XM\_098505) is another VGAM384 host target gene. LOC154282 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154282, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154282 BINDING SITE, designated SEQ ID:41697, to the nucleotide sequence of VGAM384 RNA, herein designated VGAM RNA, also designated SEQ ID:3095.

[19058] Another function of VGAM384 is therefore inhibition of LOC154282 (Accession XM\_098505). Accordingly, utilities of VGAM384 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC154282. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 385 (VGAM385) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19059] VGAM385 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM385 was detected is described hereinabove with reference to Figs. 1–8.

[19060] VGAM385 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis A Virus. VGAM385 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19061] VGAM385 gene encodes a VGAM385 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM385 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM385 precursor RNA is designated SEQ

ID:371, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:371 is located at position 3807 relative to the genome of Hepatitis A Virus.

[19062] VGAM385 precursor RNA folds onto itself, forming VGAM385 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19063] An enzyme complex designated DICER COMPLEX, `dices` the VGAM385 folded precursor RNA into VGAM385 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 53%) nucleotide sequence of VGAM385 RNA is designated SEQ ID:3096, and is provided hereinbelow with reference to the sequence

listing part.

[19064] VGAM385 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM385 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM385 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19065] VGAM385 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM385 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM385 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM385 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM385 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19066] The complementary binding of VGAM385 RNA, herein designated VGAM RNA, to host target binding sites on VGAM385 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM385 host target RNA into VGAM385 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19067] It is appreciated that VGAM385 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM385 host target genes. The mRNA of each one of this plurality of VGAM385 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM385 RNA, herein designated VGAM



RNA, and which when bound by VGAM385 RNA causes inhibition of translation of respective one or more VGAM385 host target proteins.

[19068] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM385 gene, herein designated VGAM GENE, on one or more VGAM385 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19069] It is yet further appreciated that a function of VGAM385 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM385 include diagnosis, prevention and treatment of viral infection by Hepatitis A Virus. Specific functions, and accordingly utilities, of VGAM385 correlate with, and may be deduced from, the identity of the host target genes which VGAM385 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19070] Nucleotide sequences of the VGAM385 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM385 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM385 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM385 are further described hereinbelow with reference to Table 1.

[19071] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM385 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM385 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19072] As mentioned hereinabove with reference to Fig. 1, a function of VGAM385 gene, herein designated VGAM is

inhibition of expression of VGAM385 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM385 correlate with, and may be deduced from, the identity of the target genes which VGAM385 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19073] Lipase A, Lysosomal Acid, Cholesterol Esterase (Wolman disease) (LIPA, Accession NM\_000235) is a VGAM385 host target gene. LIPA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LIPA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LIPA BINDING SITE, designated SEQ ID:5745, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19074] A function of VGAM385 is therefore inhibition of Lipase A, Lysosomal Acid, Cholesterol Esterase (Wolman disease) (LIPA, Accession NM\_000235). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LIPA. DKFZP434E2135 (Accession NM\_030804) is another VGAM385 host target gene. DKFZP434E2135 BINDING

SITE is HOST TARGET binding site found in the 3` un-translated region of mRNA encoded by DKFZP434E2135, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434E2135 BINDING SITE, designated SEQ ID:25113, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19075] Another function of VGAM385 is therefore inhibition of DKFZP434E2135 (Accession NM\_030804). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434E2135. FLJ10232 (Accession NM\_018033) is another VGAM385 host target gene. FLJ10232 BINDING SITE is HOST TARGET binding site found in the 3` un-translated region of mRNA encoded by FLJ10232, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10232 BINDING SITE, designated SEQ ID:19773, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19076] Another function of VGAM385 is therefore inhibition of FLJ10232 (Accession NM\_018033). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10232. FLJ10687 (Accession NM\_018178) is another VGAM385 host target gene. FLJ10687 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10687 BINDING SITE, designated SEQ ID:20007, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19077] Another function of VGAM385 is therefore inhibition of FLJ10687 (Accession NM\_018178). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10687. FLJ10813 (Accession NM\_018229) is another VGAM385 host target gene. FLJ10813 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10813, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10813 BINDING SITE, designated SEQ ID:20167, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19078] Another function of VGAM385 is therefore inhibition of FLJ10813 (Accession NM\_018229). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10813. FLJ13912 (Accession NM\_022770) is another VGAM385 host target gene. FLJ13912 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13912, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13912 BINDING SITE, designated SEQ ID:23027, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19079] Another function of VGAM385 is therefore inhibition of FLJ13912 (Accession NM\_022770). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13912.

FLJ20519 (Accession NM\_017860) is another VGAM385 host target gene. FLJ20519 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20519 BINDING SITE, designated SEQ ID:19537, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19080] Another function of VGAM385 is therefore inhibition of FLJ20519 (Accession NM\_017860). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20519. KIAA0217 (Accession XM\_040265) is another VGAM385 host target gene. KIAA0217 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0217, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0217 BINDING SITE, designated SEQ ID:33276, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3096.

[19081] Another function of VGAM385 is therefore inhibition of KIAA0217 (Accession XM\_040265). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0217. KIAA0417 (Accession XM\_048898) is another VGAM385 host target gene. KIAA0417 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0417, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0417 BINDING SITE, designated SEQ ID:35287, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19082] Another function of VGAM385 is therefore inhibition of KIAA0417 (Accession XM\_048898). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0417. KIAA0451 (Accession NM\_014826) is another VGAM385 host target gene. KIAA0451 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0451, corresponding to



a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0451 BINDING SITE, designated SEQ ID:16806, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19083] Another function of VGAM385 is therefore inhibition of KIAA0451 (Accession NM\_014826). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0451. KIAA1500 (Accession XM\_034353) is another VGAM385 host target gene. KIAA1500 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1500 BINDING SITE, designated SEQ ID:32066, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19084] Another function of VGAM385 is therefore inhibition of KIAA1500 (Accession XM\_034353). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1500. Oculomedin (OCLM, Accession NM\_022375) is another VGAM385 host target gene. OCLM BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by OCLM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OCLM BINDING SITE, designated SEQ ID:22762, to the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19085] Another function of VGAM385 is therefore inhibition of Oculomedin (OCLM, Accession NM\_022375). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OCLM. LOC151475 (Accession XM\_098063) is another VGAM385 host target gene. LOC151475 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC151475, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151475 BINDING SITE, designated SEQ ID:41357, to

the nucleotide sequence of VGAM385 RNA, herein designated VGAM RNA, also designated SEQ ID:3096.

[19086] Another function of VGAM385 is therefore inhibition of LOC151475 (Accession XM\_098063). Accordingly, utilities of VGAM385 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151475. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 386 (VGAM386) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19087] VGAM386 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM386 was detected is described hereinabove with reference to Figs. 1–8.

[19088] VGAM386 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis A Virus. VGAM386 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19089] VGAM386 gene encodes a VGAM386 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM386 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM386 precursor RNA is designated SEQ ID:372, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:372 is located at position 1168 relative to the genome of Hepatitis A Virus.

[19090] VGAM386 precursor RNA folds onto itself, forming VGAM386 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19091] An enzyme complex designated DICER COMPLEX, `dices` the VGAM386 folded precursor RNA into VGAM386 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM386 RNA is designated SEQ ID:3097, and is provided hereinbelow with reference to the sequence listing part.

[19092] VGAM386 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM386 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM386 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[19093] VGAM386 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM386 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM386 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM386 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM386 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19094] The complementary binding of VGAM386 RNA, herein designated VGAM RNA, to host target binding sites on VGAM386 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM386 host target RNA into VGAM386 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19095] It is appreciated that VGAM386 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM386 host target genes. The mRNA of each one of this plurality of VGAM386 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM386 RNA, herein designated VGAM RNA, and which when bound by VGAM386 RNA causes inhibition of translation of respective one or more VGAM386 host target proteins.

[19096] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM386 gene, herein designated VGAM GENE, on one or more VGAM386 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[19097] It is yet further appreciated that a function of VGAM386 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of viral infection by Hepatitis A Virus. Specific functions, and accordingly utilities, of VGAM386 correlate with, and may be deduced from, the identity of the host target genes which VGAM386 binds and inhibits, and the function of these host target genes, as elaborated herein—below.

[19098] Nucleotide sequences of the VGAM386 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM386 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM386 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM386 are further described hereinbelow with reference to Table 1.

[19099] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM386 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM386 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19100] As mentioned hereinabove with reference to Fig. 1, a function of VGAM386 gene, herein designated VGAM is inhibition of expression of VGAM386 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM386 correlate with, and may be deduced from, the identity of the target genes which VGAM386 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19101] Estrogen-related Receptor Beta Like 1 (ESRRBL1, Accession NM\_018010) is a VGAM386 host target gene. ESR-RBL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESRRBL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRBL1 BINDING SITE, designated SEQ ID:19739, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19102] A function of VGAM386 is therefore inhibition of Estro-

gen-related Receptor Beta Like 1 (ESRRBL1, Accession NM\_018010). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESRRBL1. Growth Differentiation Factor 8 (GDF8, Accession NM\_005259) is another VGAM386 host target gene. GDF8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GDF8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GDF8 BINDING SITE, designated SEQ ID:11766, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19103] Another function of VGAM386 is therefore inhibition of Growth Differentiation Factor 8 (GDF8, Accession NM\_005259), a gene which acts specifically as a negative regulator of skeletal muscle growth. Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GDF8. The function of GDF8 has been established by previous studies. The transforming growth factor-beta superfamily encompasses a large number of growth and differentia-

tion factors that play important roles in regulating embryonic development and in maintaining tissue homeostasis in adult animals. GDF8, or myostatin, is a member of this superfamily with a role in the control and maintenance of skeletal muscle mass. Animal model experiments lend further support to the function of GDF8. To determine the biologic function of Gdf8, McPherron et al. (1997) disrupted the Gdf8 gene by gene targeting in mice. Gdf8-null animals were significantly larger than wildtype animals and showed a large and widespread increase in skeletal muscle mass. Individual muscles of mutant animals weighed 2 to 3 times more than those of wildtype animals, and the increase in mass appeared to result from a combination of muscle cell hyperplasia and hypertrophy. McPherron et al. (1997) suggested that Gdf8 functions specifically as a negative regulator of skeletal muscle growth. Lin et al. (2002) observed increased skeletal muscle mass in their myostatin-null mouse model compared to wildtype animals as early as 4 weeks of age. In addition, the mutant mice showed reduced production and secretion of leptin (OMIM Ref. No. 164160) which was associated with reduced fat deposition. The reduced adipogenesis in the knockout mice suggested that myostatin is

involved in regulating adiposity as well as muscularity.

[19104] It is appreciated that the abovementioned animal model for GDF8 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[19105] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19106] Gonzalez–Cadavid, N. F.; Taylor, W. E.; Yarasheski, K.; Sinha–Hikim, I.; Ma, K.; Ezzat, S.; Shen, R.; Lalani, R.; Asa, S.; Mamita, M.; Nair, G.; Arver, S.; Bhasin, S. : Organization of the human myostatin gene and expression in healthy men and HIV–infected men with muscle wasting. Proc. Nat. Acad. Sci. 95: 14938–14943, 1998. ; and

[19107] Lin, J.; Arnold, H. B.; Della–Fera, M. A.; Azain, M. J.; Hartzell, D. L.; Baile, C. A. : Myostatin knockout in mice increases myogenesis and decreases adipogenesis. Biochem. Biophys. Res.

[19108] Further studies establishing the function and utilities of GDF8 are found in John Hopkins OMIM database record ID 601788, and in cited publications numbered 1280–1283, 8868–8869, 421 and 9109–5789 listed in the bibliography section hereinbelow, which are also hereby incorpo–

rated by reference. Heparan Sulfate (glucosamine) 3-O-sulfotransferase 4 (HS3ST4, Accession XM\_056254) is another VGAM386 host target gene. HS3ST4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HS3ST4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HS3ST4 BINDING SITE, designated SEQ ID:36369, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19109] Another function of VGAM386 is therefore inhibition of Heparan Sulfate (glucosamine) 3-O-sulfotransferase 4 (HS3ST4, Accession XM\_056254). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HS3ST4. MADS Box Transcription Enhancer Factor 2, Polypeptide C (myocyte enhancer factor 2C) (MEF2C, Accession NM\_002397) is another VGAM386 host target gene. MEF2C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MEF2C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of MEF2C BINDING SITE, designated SEQ ID:8211, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19110] Another function of VGAM386 is therefore inhibition of MADS Box Transcription Enhancer Factor 2, Polypeptide C (myocyte enhancer factor 2C) (MEF2C, Accession NM\_002397), a gene which regulates muscle-specific and mitogen-inducible genes. Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEF2C. The function of MEF2C has been established by previous studies. The MEF2 family of regulatory proteins are, like the myogenic basic helix-loop-helix proteins (e.g., 159970), involved in myogenesis; see MEF2A (OMIM Ref. No. 600660). McDermott et al. (1993) cloned a member of the MEF2 family of proteins from a human skeletal muscle cDNA library using a fragment of the MEF2A cDNA as a probe. Transcripts of MEF2C were found in the skeletal muscle and brain. Alternative splice variants were found, 1 of which was unique to the brain. Leifer et al. (1993) found that the brain form was expressed by neurons in

particular layers of the cerebral cortex and that expression declined during postnatal development. The skeletal isoform of the cDNA encodes a 465-amino acid protein with conserved MADS and MEF2 domains. Like the other MEF2 gene products, MEF2C has both DNA binding and trans-activating activities indistinguishable from other members of the family. MEF2C, however, is induced late during myogenic differentiation and has a strict tissue-specific pattern of expression not seen in MEF2A or MEF2B. Breitbart et al. (1993) suggested that, while MEF2A may be involved in induction of muscle differentiation, MEF2C may be involved with maintenance of the differentiated state. CREB-binding protein (CBP; 600140)/p300 (OMIM Ref. No. 602700) and p300/CBP-associated factor (PCAF; 602203) are coactivators for MEF2C during differentiation. Chen et al. (2000) showed that NCOA2 mediates the coactivation of MEF2C-dependent transcription through interaction with the MADS box domain of MEF2C. They proposed a model of cooperative interaction between NCOA2, myogenin (MYOG; 159980), and MEF2C in the regulation of muscle-specific gene expression. During mammalian development, electrical activity promotes the calcium-dependent survival of neurons that have made

appropriate synaptic connections. Mao et al. (1999) showed that calcium influx into cerebellar neurons triggers the activation of the MKK6 (OMIM Ref. No. 601254)–p38 MAP kinase (OMIM Ref. No. 600289) cascade and that the p38 MAP kinase then phosphorylates and activates MEF2s. Once activated by this calcium-dependent p38 MAP kinase signaling pathway, MEF2 can regulate the expression of genes that are critical for survival of newly differentiated neurons. These findings demonstrated that MEF2 is a calcium-regulated transcription factor and defined a function for MEF2 during nervous system development that is distinct from previously well-characterized functions of MEF2 during muscle differentiation. Martin et al. (1994) mapped Mef2 to mouse chromosome 13. By fluorescence in situ hybridization, Krainc et al. (1995) mapped human MEF2C to 5q14, a region with homology of synteny to the mouse location. Members of the MEF2 family of MADs–box transcription factors bind to an A–T–rich DNA sequence associated with muscle-specific genes. The murine MEF2C gene is expressed in heart precursor cells before formation of the linear heart tube. In mice homozygous for a known mutation of MEF2C, Lin et al. (1997) found that the heart tube



did not undergo looping morphogenesis, the future right ventricle did not form, and a subset of cardiac muscle genes was not expressed. The absence of the right ventricular region of the mutant correlated with downregulation of the dHAND gene, which encodes a basic helix-loop-helix transcription factor required for cardiac morphogenesis. The authors concluded that MEF2C is an essential regulator of cardiac morphogenesis and right ventricular development.

[19111] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19112] Breitbart, R. E.; Liang, C.; Smoot, L. B.; Laheru, D. A.; Mahdavi, V.; Nadal-Ginard, B. : A fourth human MEF2 transcription factor, hMEF2D, is an early marker of the myogenic lineage. *Development* 118: 1095-1106, 1993. ; and

[19113] Chen, S. L.; Dowhan, D. H.; Hosking, B. M.; Muscat, G. E. O. : The steroid receptor coactivator, GRIP-1, is necessary for MEF-2C-dependent gene expression and skeletal muscle differenti.

[19114] Further studies establishing the function and utilities of MEF2C are found in John Hopkins OMIM database record ID 600662, and in cited publications numbered 8293,

8303–8304, 7159, 8295–829 and 7243 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SIP (Accession NM\_014412) is another VGAM386 host target gene. SIP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIP BINDING SITE, designated SEQ ID:15757, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19115] Another function of VGAM386 is therefore inhibition of SIP (Accession NM\_014412). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIP. DKFZp434C0328 (Accession NM\_017577) is another VGAM386 host target gene. DKFZp434C0328 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp434C0328, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se–

quences of DKFZp434C0328 BINDING SITE, designated SEQ ID:19013, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19116] Another function of VGAM386 is therefore inhibition of DKFZp434C0328 (Accession NM\_017577). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434C0328. FLJ10307 (Accession NM\_018053) is another VGAM386 host target gene. FLJ10307 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10307, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10307 BINDING SITE, designated SEQ ID:19813, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19117] Another function of VGAM386 is therefore inhibition of FLJ10307 (Accession NM\_018053). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10307. KIAA0237 (Accession NM\_014747) is another VGAM386

host target gene. KIAA0237 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0237 BINDING SITE, designated SEQ ID:16437, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19118] Another function of VGAM386 is therefore inhibition of KIAA0237 (Accession NM\_014747). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0237. KIAA1466 (Accession XM\_050285) is another VGAM386 host target gene. KIAA1466 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1466, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1466 BINDING SITE, designated SEQ ID:35602, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19119] Another function of VGAM386 is therefore inhibition of KIAA1466 (Accession XM\_050285). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1466. Kv6.3 (Accession NM\_133490) is another VGAM386 host target gene. Kv6.3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by Kv6.3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Kv6.3 BINDING SITE, designated SEQ ID:28563, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19120] Another function of VGAM386 is therefore inhibition of Kv6.3 (Accession NM\_133490). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Kv6.3. LOC145566 (Accession XM\_085174) is another VGAM386 host target gene. LOC145566 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145566, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145566 BINDING SITE, designated SEQ ID:37898, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19121] Another function of VGAM386 is therefore inhibition of LOC145566 (Accession XM\_085174). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145566. LOC220766 (Accession XM\_165471) is another VGAM386 host target gene. LOC220766 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220766, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220766 BINDING SITE, designated SEQ ID:43653, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19122] Another function of VGAM386 is therefore inhibition of LOC220766 (Accession XM\_165471). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC220766. LOC253959 (Accession XM\_170749) is another VGAM386 host target gene. LOC253959 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253959, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253959 BINDING SITE, designated SEQ ID:45507, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19123] Another function of VGAM386 is therefore inhibition of LOC253959 (Accession XM\_170749). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253959. LOC257438 (Accession XM\_168338) is another VGAM386 host target gene. LOC257438 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257438, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257438 BINDING SITE, designated SEQ ID:45107, to the nucleotide sequence of VGAM386 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3097.

[19124] Another function of VGAM386 is therefore inhibition of LOC257438 (Accession XM\_168338). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257438. LOC91012 (Accession XM\_035503) is another VGAM386 host target gene. LOC91012 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91012, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91012 BINDING SITE, designated SEQ ID:32283, to the nucleotide sequence of VGAM386 RNA, herein designated VGAM RNA, also designated SEQ ID:3097.

[19125] Another function of VGAM386 is therefore inhibition of LOC91012 (Accession XM\_035503). Accordingly, utilities of VGAM386 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91012. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 387 (VGAM387) viral gene, which modu-



lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19126] VGAM387 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM387 was detected is described hereinabove with reference to Figs. 1–8.

[19127] VGAM387 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 1. VGAM387 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19128] VGAM387 gene encodes a VGAM387 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM387 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM387 precursor RNA is designated SEQ ID:373, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:373 is located at position 97453 relative to the genome of Equine Herpesvirus 1.

[19129] VGAM387 precursor RNA folds onto itself, forming

VGAM387 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19130] An enzyme complex designated DICER COMPLEX, `dices` the VGAM387 folded precursor RNA into VGAM387 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM387 RNA is designated SEQ ID:3098, and is provided hereinbelow with reference to the sequence listing part.

[19131] VGAM387 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM387 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM387 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19132] VGAM387 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM387 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM387 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM387 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM387 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19133] The complementary binding of VGAM387 RNA, herein designated VGAM RNA, to host target binding sites on VGAM387 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM387 host target RNA into VGAM387 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19134] It is appreciated that VGAM387 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM387 host target genes. The mRNA of each one of this plurality of VGAM387 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM387 RNA, herein designated VGAM RNA, and which when bound by VGAM387 RNA causes inhibition of translation of respective one or more VGAM387 host target proteins.

[19135] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM387 gene, herein designated VGAM GENE, on one or more VGAM387 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19136] It is yet further appreciated that a function of VGAM387 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM387 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM387 correlate with, and may be deduced from, the identity of the host target genes which VGAM387 binds and inhibits, and

the function of these host target genes, as elaborated hereinbelow.

[19137] Nucleotide sequences of the VGAM387 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM387 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM387 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM387 are further described hereinbelow with reference to Table 1.

[19138] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM387 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM387 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19139] As mentioned hereinabove with reference to Fig. 1, a function of VGAM387 gene, herein designated VGAM is inhibition of expression of VGAM387 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM387 correlate with, and may be deduced from, the identity of the target genes which VGAM387 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[19140] A Disintegrin and Metalloproteinase Domain 11 (ADAM11, Accession NM\_002390) is a VGAM387 host target gene. ADAM11 BINDING SITE1 and ADAM11 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ADAM11, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM11 BINDING SITE1 and ADAM11 BINDING SITE2, designated SEQ ID:8206 and SEQ ID:22239 respectively, to the nucleotide sequence of VGAM387 RNA, herein designated VGAM RNA, also designated SEQ ID:3098.

[19141] A function of VGAM387 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 11 (ADAM11, Accession NM\_002390), a gene which Member of the ADAM family of zinc metalloproteases. Accordingly, utilities of VGAM387 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM11. The function of ADAM11 has been established by previous studies. From chromosomal region 17q21.3, where a tumor suppressor gene for breast and ovarian cancers is thought to reside, Emi et al. (1993) isolated a novel gene

from a cosmid clone that showed somatic rearrangements in 2 breast cancers. The gene encoded a 524-amino acid metalloproteinase-like, disintegrin-like, and cysteine-rich (MDC) protein with sequence similarity to members of the snake-venom metalloprotease/disintegrin family and guinea-pig sperm-surface protein PH-30 (OMIM Ref. No. 601533). These proteins have been implicated in cell-cell or cell-extracellular matrix interactions. Rearrangements in both tumors involved multiple exons and disrupted the coding region of the gene. Sagane et al. (1998) noted that MDC is a member of the cellular disintegrin, or ADAM (a disintegrin and metalloproteinase), family. See ADAM20 (OMIM Ref. No. 603712). They isolated cDNAs encoding 2 related human proteins, MDC2 (OMIM Ref. No. 603709) and MDC3 (OMIM Ref. No. 603710). Northern blot analysis revealed that, like the MDC2 and MDC3 mRNAs, the 5-kb MDC transcript was expressed predominantly in brain.

[19142] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19143] Emi, M.; Katagiri, T.; Harada, Y.; Saito, H.; Inazawa, J.; Ito, I.; Kasumi, F.; Nakamura, Y. : A novel metalloprotease/disintegrin-like gene at 17q21.3 is somatically rearranged in two



primary breast cancers. Nature Genet. 5: 151–157, 1993. ;  
and

[19144] Sagane, K.; Ohya, Y.; Hasegawa, Y.; Tanaka, I. : Metallo–proteinase–like, disintegrin–like, cysteine–rich proteins MDC2 and MDC3: novel human cellular disintegrins highly expressed in the.

[19145] Further studies establishing the function and utilities of ADAM11 are found in John Hopkins OMIM database record ID 155120, and in cited publications numbered 11102–1110 and 11444 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 388 (VGAM388) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19146] VGAM388 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM388 was detected is described hereinabove with reference to Figs. 1–8.

[19147] VGAM388 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Equine Herpesvirus 1. VGAM388 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19148] VGAM388 gene encodes a VGAM388 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM388 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM388 precursor RNA is designated SEQ ID:374, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:374 is located at position 97176 relative to the genome of Equine Herpesvirus 1.

[19149] VGAM388 precursor RNA folds onto itself, forming VGAM388 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19150] An enzyme complex designated DICER COMPLEX, `dices` the VGAM388 folded precursor RNA into VGAM388 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 68%) nucleotide sequence of VGAM388 RNA is designated SEQ ID:3099, and is provided hereinbelow with reference to the sequence listing part.

[19151] VGAM388 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM388 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM388 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19152] VGAM388 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM388 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM388 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM388 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM388 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19153] The complementary binding of VGAM388 RNA, herein designated VGAM RNA, to host target binding sites on VGAM388 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM388 host tar-

get RNA into VGAM388 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19154] It is appreciated that VGAM388 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM388 host target genes. The mRNA of each one of this plurality of VGAM388 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM388 RNA, herein designated VGAM RNA, and which when bound by VGAM388 RNA causes inhibition of translation of respective one or more VGAM388 host target proteins.

[19155] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM388 gene, herein designated VGAM GENE, on one or more VGAM388 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19156] It is yet further appreciated that a function of VGAM388 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM388 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM388 correlate with, and may be deduced from, the identity of the host target genes which VGAM388 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19157] Nucleotide sequences of the VGAM388 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM388 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM388 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM388 are further

described hereinbelow with reference to Table 1.

[19158] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM388 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM388 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19159] As mentioned hereinabove with reference to Fig. 1, a function of VGAM388 gene, herein designated VGAM is inhibition of expression of VGAM388 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM388 correlate with, and may be deduced from, the identity of the target genes which VGAM388 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19160] Leucine-rich Repeat-containing 2 (LRRC2, Accession NM\_024512) is a VGAM388 host target gene. LRRC2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LRRC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LRRC2 BINDING SITE, designated SEQ ID:23704, to the nucleotide sequence of VGAM388 RNA, herein designated VGAM RNA, also designated SEQ ID:3099.

[19161] A function of VGAM388 is therefore inhibition of Leucine-rich Repeat-containing 2 (LRRC2, Accession NM\_024512). Accordingly, utilities of VGAM388 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRRC2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 389 (VGAM389) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19162] VGAM389 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM389 was detected is described hereinabove with reference to Figs. 1–8.

[19163] VGAM389 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 1. VGAM389 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.



[19164] VGAM389 gene encodes a VGAM389 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM389 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM389 precursor RNA is designated SEQ ID:375, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:375 is located at position 99186 relative to the genome of Equine Herpesvirus 1.

[19165] VGAM389 precursor RNA folds onto itself, forming VGAM389 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19166] An enzyme complex designated DICER COMPLEX, `dices` the VGAM389 folded precursor RNA into VGAM389 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM389 RNA is designated SEQ ID:3100, and is provided hereinbelow with reference to the sequence listing part.

[19167] VGAM389 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM389 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM389 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19168] VGAM389 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM389 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM389 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM389 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM389 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[19169] The complementary binding of VGAM389 RNA, herein designated VGAM RNA, to host target binding sites on VGAM389 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM389 host target RNA into VGAM389 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19170] It is appreciated that VGAM389 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM389 host target genes. The mRNA of each one of this plurality of VGAM389 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM389 RNA, herein designated VGAM RNA, and which when bound by VGAM389 RNA causes inhibition of translation of respective one or more VGAM389 host target proteins.

[19171] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM389 gene, herein designated VGAM GENE, on one or more VGAM389 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19172] It is yet further appreciated that a function of VGAM389 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM389 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM389 correlate with, and may be deduced from, the identity of the host target genes which VGAM389 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19173] Nucleotide sequences of the VGAM389 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM389 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM389 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM389 are further described hereinbelow with reference to Table 1.

[19174] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM389 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM389 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19175] As mentioned hereinabove with reference to Fig. 1, a function of VGAM389 gene, herein designated VGAM is inhibition of expression of VGAM389 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM389 correlate with, and may be deduced from, the identity of the target genes which VGAM389 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19176] ATPase, Ca++ Transporting, Cardiac Muscle, Slow Twitch 2 (ATP2A2, Accession NM\_001681) is a VGAM389 host target gene. ATP2A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP2A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP2A2 BINDING SITE, designated SEQ ID:7400, to the nucleotide sequence of VGAM389 RNA, herein designated VGAM RNA, also designated SEQ ID:3100.

[19177] A function of VGAM389 is therefore inhibition of ATPase, Ca++ Transporting, Cardiac Muscle, Slow Twitch 2 (ATP2A2, Accession NM\_001681). Accordingly, utilities of VGAM389 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP2A2. Guanine Nucleotide Binding Protein (G protein), Beta Polypeptide 2 (GNB2, Accession NM\_005273) is another VGAM389 host target gene. GNB2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GNB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GNB2 BINDING SITE, designated SEQ ID:11777, to the nucleotide sequence of VGAM389 RNA, herein designated VGAM RNA, also designated SEQ ID:3100.

[19178] Another function of VGAM389 is therefore inhibition of Guanine Nucleotide Binding Protein (G protein), Beta Polypeptide 2 (GNB2, Accession NM\_005273). Accordingly, utilities of VGAM389 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNB2. Histone Deacetylase 4 (HDAC4, Accession NM\_006037) is another VGAM389 host target gene.

HDAC4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HDAC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HDAC4 BINDING SITE, designated SEQ ID:12660, to the nucleotide sequence of VGAM389 RNA, herein designated VGAM RNA, also designated SEQ ID:3100.

[19179] Another function of VGAM389 is therefore inhibition of Histone Deacetylase 4 (HDAC4, Accession NM\_006037), a gene which is responsible for the deacetylation of lysine residues on the n-terminal part of the core histones and may mediate transcriptional regulation. Accordingly, utilities of VGAM389 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HDAC4. The function of HDAC4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM264.FLJ20699 (Accession NM\_017931) is another VGAM389 host target gene. FLJ20699 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20699, corre-



sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20699 BINDING SITE, designated SEQ ID:19618, to the nucleotide sequence of VGAM389 RNA, herein designated VGAM RNA, also designated SEQ ID:3100.

[19180] Another function of VGAM389 is therefore inhibition of FLJ20699 (Accession NM\_017931). Accordingly, utilities of VGAM389 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20699. MGC15937 (Accession NM\_080661) is another VGAM389 host target gene. MGC15937 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC15937, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15937 BINDING SITE, designated SEQ ID:27948, to the nucleotide sequence of VGAM389 RNA, herein designated VGAM RNA, also designated SEQ ID:3100.

[19181] Another function of VGAM389 is therefore inhibition of MGC15937 (Accession NM\_080661). Accordingly, utilities of VGAM389 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with MGC15937. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 390 (VGAM390) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19182] VGAM390 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM390 was detected is described hereinabove with reference to Figs. 1–8.

[19183] VGAM390 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 1. VGAM390 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19184] VGAM390 gene encodes a VGAM390 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM390 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM390 precursor RNA is designated SEQ

ID:376, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:376 is located at position 98078 relative to the genome of Equine Herpesvirus 1.

[19185] VGAM390 precursor RNA folds onto itself, forming VGAM390 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19186] An enzyme complex designated DICER COMPLEX, `dices` the VGAM390 folded precursor RNA into VGAM390 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM390 RNA is designated SEQ ID:3101, and is provided hereinbelow with reference to the sequence

listing part.

[19187] VGAM390 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM390 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM390 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19188] VGAM390 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM390 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM390 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM390 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM390 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19189] The complementary binding of VGAM390 RNA, herein designated VGAM RNA, to host target binding sites on VGAM390 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM390 host target RNA into VGAM390 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19190] It is appreciated that VGAM390 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM390 host target genes. The mRNA of each one of this plurality of VGAM390 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM390 RNA, herein designated VGAM

RNA, and which when bound by VGAM390 RNA causes inhibition of translation of respective one or more VGAM390 host target proteins.

[19191] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM390 gene, herein designated VGAM GENE, on one or more VGAM390 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19192] It is yet further appreciated that a function of VGAM390 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM390 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM390 correlate with, and may be deduced from, the identity of the host target genes which VGAM390 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19193] Nucleotide sequences of the VGAM390 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM390 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM390 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM390 are further described hereinbelow with reference to Table 1.

[19194] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM390 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM390 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19195] As mentioned hereinabove with reference to Fig. 1, a function of VGAM390 gene, herein designated VGAM is

inhibition of expression of VGAM390 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM390 correlate with, and may be deduced from, the identity of the target genes which VGAM390 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19196] Alkaline Phosphatase, Placental-like 2 (ALPPL2, Accession XM\_044139) is a VGAM390 host target gene. ALPPL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALPPL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALPPL2 BINDING SITE, designated SEQ ID:34139, to the nucleotide sequence of VGAM390 RNA, herein designated VGAM RNA, also designated SEQ ID:3101.

[19197] A function of VGAM390 is therefore inhibition of Alkaline Phosphatase, Placental-like 2 (ALPPL2, Accession XM\_044139). Accordingly, utilities of VGAM390 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALPPL2. Ephrin-B1 (EFNB1, Accession NM\_004429) is another VGAM390 host target gene. EFNB1 BINDING SITE is HOST TARGET binding site



found in the 3' untranslated region of mRNA encoded by EFNB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EFNB1 BINDING SITE, designated SEQ ID:10708, to the nucleotide sequence of VGAM390 RNA, herein designated VGAM RNA, also designated SEQ ID:3101.

[19198] Another function of VGAM390 is therefore inhibition of Ephrin-B1 (EFNB1, Accession NM\_004429), a gene which is a transmembrane ligand of Eph-related receptor tyrosine kinases, has a role in cell adhesion. Accordingly, utilities of VGAM390 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EFNB1. The function of EFNB1 has been established by previous studies. Bohme et al. (1996) presented evidence that LERK2 is a functional ligand of the EPH-related kinase HEK2 (EPHB3; 601839). They reported that coincubation of HEK2- and LERK2-expressing cells induces cell-cell adhesion and aggregation. Palmer et al. (2002) showed that SRC family kinases, or SFKs (see OMIM Ref. No. SRC; 190090), are positive regulators of ephrin-B phosphorylation and phosphotyrosine-mediated reverse signaling.

EphB receptor engagement of ephrin-B caused rapid recruitment of SFKs to ephrin-B expression domains and transient SFK activation. With delayed kinetics, ephrin-B ligands recruited the cytoplasmic PDZ domain-containing protein tyrosine phosphatase PTPBL (see OMIM Ref. No. 600267) and were dephosphorylated. These data suggested the presence of a switch mechanism that allows a shift from phosphotyrosine-/SFK-dependent signaling to PDZ-dependent signaling.

[19199] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19200] Bohme, B.; VandenBos, T.; Cerretti, D. P.; Park, L. S.; Holtrich, U.; Rubsamen-Waigmann, H.; Strebhardt, K. : Cell-cell adhesion mediated by binding of membrane-anchored ligand LERK-2 to the EPH-related receptor human embryonal kinase 2 promotes tyrosine kinase activity. J. Biol. Chem. 271: 24747-24752, 1996. ; and

[19201] Palmer, A.; Zimmer, M.; Erdmann, K. S.; Eulenburg, V.; Porthin, A.; Heumann, R.; Deutsch, U.; Klein, R. : EphrinB phosphorylation and reverse signaling: regulation by Src kinases and PTP.

[19202] Further studies establishing the function and utilities of

EFNB1 are found in John Hopkins OMIM database record ID 300035, and in cited publications numbered 8710–8713 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. 8-oxoguanine DNA Glycosylase (OGG1, Accession NM\_016819) is another VGAM390 host target gene. OGG1 BINDING SITE1 through OGG1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by OGG1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OGG1 BINDING SITE1 through OGG1 BINDING SITE3, designated SEQ ID:18809, SEQ ID:8392 and SEQ ID:18814 respectively, to the nucleotide sequence of VGAM390 RNA, herein designated VGAM RNA, also designated SEQ ID:3101.

[19203] Another function of VGAM390 is therefore inhibition of 8-oxoguanine DNA Glycosylase (OGG1, Accession NM\_016819), a gene which is involved in base excision DNA repair and removal of 8-oxyguanine. Accordingly, utilities of VGAM390 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OGG1. The function of OGG1 has been established by

previous studies. The major mutagenic base lesion in DNA caused by exposure to reactive oxygen species is 8-oxoguanine. This damaged base is excised by a DNA glycosylase with an associated lyase activity for chain cleavage. Lu et al. (1997), Aburatani et al. (1997), Bjoras et al. (1997), Rosenquist et al. (1997), Radicella et al. (1997), and Roldan-Arjona et al. (1997) cloned human cDNAs with partial sequence homology to the yeast 8-oxoguanine DNA glycosylase (OGG1) gene. Radicella et al. (1997) found that the predicted protein has 345 amino acids and a calculated molecular mass of 39 kD. Roldan-Arjona et al. (1997), who called the enzyme 8-hydroxyguanine DNA glycosylase, estimated their 424-amino acid predicted human enzyme to have a size of 47 kD. They showed that it releases free 8-hydroxyguanine from oxidized DNA and introduces a chain break in a double-stranded oligonucleotide specifically at an 8-hydroxyguanine residue base-paired with cytosine. Expression of the human protein in a DNA repair-deficient *E. coli* strain partly suppressed its spontaneous mutator phenotype. Radicella et al. (1997) showed that when the human coding sequence was expressed in a yeast strain mutant in *Ogg1*, it was able to complement

the spontaneous mutator phenotype. Arai et al. (1997) also cloned the human OGG1 gene and, by Northern blotting, showed that the gene is ubiquitously expressed in a variety of human organs. By fluorescence in situ hybridization, Roldan-Arjona et al. (1997) and Radicella et al. (1997) mapped the human OGG1 gene to 3p25 (3p25.3-p25.2). By the same method, Arai et al. (1997) mapped the OGG1 gene to 3p26.2. By radiation hybrid analysis, Ishida et al. (1999) mapped the gene to 3p26, proximal to the VHL gene (OMIM Ref. No. 193300).

[19204] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19205] Radicella, J. P.; Dherin, C.; Desmaze, C.; Fox, M. S.; Boiteux, S. : Cloning and characterization of hOGG1, a human homolog of the OGG1 gene of *Saccharomyces cerevisiae*. Proc. Nat. Acad. Sci. 94: 8010-8015, 1997. ; and

[19206] Roldan-Arjona, T.; Wei, Y.-F.; Carter, K. C.; Klungland, A.; Anselmino, C.; Wang, R.-P.; Augustus, M.; Lindahl, T. : Molecular cloning and functional expression of a human cDNA encodin.

[19207] Further studies establishing the function and utilities of OGG1 are found in John Hopkins OMIM database record ID

601982, and in cited publications numbered 1214–1222, 887 and 8892–8893 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA1193 (Accession XM\_041843) is another VGAM390 host target gene. KIAA1193 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1193, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1193 BINDING SITE, designated SEQ ID:33581, to the nucleotide sequence of VGAM390 RNA, herein designated VGAM RNA, also designated SEQ ID:3101.

[19208] Another function of VGAM390 is therefore inhibition of KIAA1193 (Accession XM\_041843). Accordingly, utilities of VGAM390 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1193. MGC2835 (Accession NM\_024072) is another VGAM390 host target gene. MGC2835 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2835, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of MGC2835 BINDING SITE, designated SEQ ID:23505, to the nucleotide sequence of VGAM390 RNA, herein designated VGAM RNA, also designated SEQ ID:3101.

[19209] Another function of VGAM390 is therefore inhibition of MGC2835 (Accession NM\_024072). Accordingly, utilities of VGAM390 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2835. LOC124044 (Accession XM\_071871) is another VGAM390 host target gene. LOC124044 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC124044, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124044 BINDING SITE, designated SEQ ID:37431, to the nucleotide sequence of VGAM390 RNA, herein designated VGAM RNA, also designated SEQ ID:3101.

[19210] Another function of VGAM390 is therefore inhibition of LOC124044 (Accession XM\_071871). Accordingly, utilities of VGAM390 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124044. LOC256158 (Accession XM\_175125) is an-

other VGAM390 host target gene. LOC256158 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256158, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256158 BINDING SITE, designated SEQ ID:46628, to the nucleotide sequence of VGAM390 RNA, herein designated VGAM RNA, also designated SEQ ID:3101.

[19211] Another function of VGAM390 is therefore inhibition of LOC256158 (Accession XM\_175125). Accordingly, utilities of VGAM390 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256158. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 391 (VGAM391) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19212] VGAM391 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM391 was detected is described



hereinabove with reference to Figs. 1–8.

[19213] VGAM391 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 1. VGAM391 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19214] VGAM391 gene encodes a VGAM391 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM391 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM391 precursor RNA is designated SEQ ID:377, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:377 is located at position 98356 relative to the genome of Equine Herpesvirus 1.

[19215] VGAM391 precursor RNA folds onto itself, forming VGAM391 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[19216] An enzyme complex designated DICER COMPLEX, `dices` the VGAM391 folded precursor RNA into VGAM391 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM391 RNA is designated SEQ ID:3102, and is provided hereinbelow with reference to the sequence listing part.

[19217] VGAM391 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM391 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM391 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19218] VGAM391 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM391 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM391 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM391 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM391 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19219] The complementary binding of VGAM391 RNA, herein designated VGAM RNA, to host target binding sites on VGAM391 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM391 host target RNA into VGAM391 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19220] It is appreciated that VGAM391 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM391 host target genes. The mRNA of each one of this plurality of VGAM391 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM391 RNA, herein designated VGAM RNA, and which when bound by VGAM391 RNA causes inhibition of translation of respective one or more VGAM391 host target proteins.

[19221] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM391 gene, herein designated VGAM GENE, on one or more VGAM391 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19222] It is yet further appreciated that a function of VGAM391 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM391 correlate with, and may be deduced from, the identity of the host target genes which VGAM391 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19223] Nucleotide sequences of the VGAM391 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM391 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM391 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM391 are further described hereinbelow with reference to Table 1.

[19224] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM391 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM391 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19225] As mentioned hereinabove with reference to Fig. 1, a function of VGAM391 gene, herein designated VGAM is inhibition of expression of VGAM391 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM391 correlate with, and may be deduced from, the identity of the target genes which VGAM391 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19226] Chemokine (C-X3-C motif) Receptor 1 (CX3CR1, Accession XM\_047502) is a VGAM391 host target gene. CX3CR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CX3CR1, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CX3CR1 BINDING SITE, designated SEQ ID:34981, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19227] A function of VGAM391 is therefore inhibition of Chemokine (C-X3-C motif) Receptor 1 (CX3CR1, Accession XM\_047502), a gene which mediates both the adhesive and migratory functions of fractalkine. Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CX3CR1. The function of CX3CR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM25. Tripartite Motif-containing 14 (TRIM14, Accession NM\_014788) is another VGAM391 host target gene. TRIM14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM14 BINDING SITE,

designated SEQ ID:16667, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19228] Another function of VGAM391 is therefore inhibition of Tripartite Motif-containing 14 (TRIM14, Accession NM\_014788), a gene which is composed of 3 zinc-binding domains and is involved in development and cell growth. Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM14. The function of TRIM14 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM180. Amyloid Beta (A4) Precursor Protein-binding, Family A, Member 2 Binding Protein (APBA2BP, Accession NM\_031232) is another VGAM391 host target gene. APBA2BP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APBA2BP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APBA2BP BINDING SITE, designated SEQ ID:25278, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM



RNA, also designated SEQ ID:3102.

[19229] Another function of VGAM391 is therefore inhibition of Amyloid Beta (A4) Precursor Protein-binding, Family A, Member 2 Binding Protein (APBA2BP, Accession NM\_031232). Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APBA2BP. FLJ13241 (Accession NM\_025088) is another VGAM391 host target gene. FLJ13241 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13241, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13241 BINDING SITE, designated SEQ ID:24711, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19230] Another function of VGAM391 is therefore inhibition of FLJ13241 (Accession NM\_025088). Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13241. KIAA0914 (Accession NM\_014883) is another VGAM391 host target gene. KIAA0914 BINDING SITE is HOST TARGET

binding site found in the 5` untranslated region of mRNA encoded by KIAA0914, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0914 BINDING SITE, designated SEQ ID:17037, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19231] Another function of VGAM391 is therefore inhibition of KIAA0914 (Accession NM\_014883). Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0914. KIAA1796 (Accession XM\_166146) is another VGAM391 host target gene. KIAA1796 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1796, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1796 BINDING SITE, designated SEQ ID:43966, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19232] Another function of VGAM391 is therefore inhibition of

KIAA1796 (Accession XM\_166146). Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1796. Septin 3 (SEPT3, Accession NM\_019106) is another VGAM391 host target gene. SEPT3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEPT3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEPT3 BINDING SITE, designated SEQ ID:21181, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19233] Another function of VGAM391 is therefore inhibition of Septin 3 (SEPT3, Accession NM\_019106). Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEPT3. LOC116437 (Accession XM\_058185) is another VGAM391 host target gene. LOC116437 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC116437, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC116437 BINDING SITE, designated SEQ ID:36583, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19234] Another function of VGAM391 is therefore inhibition of LOC116437 (Accession XM\_058185). Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116437. LOC222134 (Accession XM\_168432) is another VGAM391 host target gene. LOC222134 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC222134, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222134 BINDING SITE, designated SEQ ID:45172, to the nucleotide sequence of VGAM391 RNA, herein designated VGAM RNA, also designated SEQ ID:3102.

[19235] Another function of VGAM391 is therefore inhibition of LOC222134 (Accession XM\_168432). Accordingly, utilities of VGAM391 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222134. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 392 (VGAM392) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19236] VGAM392 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM392 was detected is described hereinabove with reference to Figs. 1–8.

[19237] VGAM392 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 1. VGAM392 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19238] VGAM392 gene encodes a VGAM392 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM392 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM392 precursor RNA is designated SEQ ID:378, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:378 is

located at position 104567 relative to the genome of Equine Herpesvirus 1.

[19239] VGAM392 precursor RNA folds onto itself, forming VGAM392 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19240] An enzyme complex designated DICER COMPLEX, `dices` the VGAM392 folded precursor RNA into VGAM392 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM392 RNA is designated SEQ ID:3103, and is provided hereinbelow with reference to the sequence listing part.

[19241] VGAM392 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM392 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM392 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[19242] VGAM392 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM392 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM392 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM392 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM392 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[19243] The complementary binding of VGAM392 RNA, herein designated VGAM RNA, to host target binding sites on VGAM392 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM392 host target RNA into VGAM392 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19244] It is appreciated that VGAM392 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM392 host target genes. The mRNA of each one of this plurality of VGAM392 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM392 RNA, herein designated VGAM RNA, and which when bound by VGAM392 RNA causes inhibition of translation of respective one or more VGAM392



host target proteins.

[19245] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM392 gene, herein designated VGAM GENE, on one or more VGAM392 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19246] It is yet further appreciated that a function of VGAM392 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM392 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 1. Spe-

cific functions, and accordingly utilities, of VGAM392 correlate with, and may be deduced from, the identity of the host target genes which VGAM392 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19247] Nucleotide sequences of the VGAM392 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM392 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM392 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM392 are further described hereinbelow with reference to Table 1.

[19248] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM392 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM392 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19249] As mentioned hereinabove with reference to Fig. 1, a function of VGAM392 gene, herein designated VGAM is inhibition of expression of VGAM392 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM392 correlate with, and may be deduced from, the identity of the target genes which VGAM392 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19250] LOC125704 (Accession XM\_058931) is a VGAM392 host target gene. LOC125704 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC125704, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC125704 BINDING SITE, designated SEQ ID:36799, to the nucleotide sequence of VGAM392 RNA, herein designated VGAM RNA, also designated SEQ ID:3103.

[19251] A function of VGAM392 is therefore inhibition of LOC125704 (Accession XM\_058931). Accordingly, utilities of VGAM392 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125704. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 393 (VGAM393) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[19252] VGAM393 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM393 was detected is described hereinabove with reference to Figs. 1–8.

[19253] VGAM393 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM393 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19254] VGAM393 gene encodes a VGAM393 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM393 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM393 precursor RNA is designated SEQ ID:379, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:379 is located at position 4681 relative to the genome of Cryphonectria Hypovirus 1.

[19255] VGAM393 precursor RNA folds onto itself, forming VGAM393 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[19256] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM393 folded precursor RNA into VGAM393 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM393 RNA is designated SEQ ID:3104, and  
is provided hereinbelow with reference to the sequence  
listing part.

[19257] VGAM393 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM393 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM393 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19258] VGAM393 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM393 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM393 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM393 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM393 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19259] The complementary binding of VGAM393 RNA, herein designated VGAM RNA, to host target binding sites on VGAM393 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM393 host target RNA into VGAM393 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19260] It is appreciated that VGAM393 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM393 host target genes. The mRNA of each one of this plurality of VGAM393 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM393 RNA, herein designated VGAM RNA, and which when bound by VGAM393 RNA causes inhibition of translation of respective one or more VGAM393 host target proteins.

[19261] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM393 gene, herein designated VGAM GENE, on one or more VGAM393 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19262] It is yet further appreciated that a function of VGAM393 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM393 correlate with, and may be deduced from, the identity of the host target genes which VGAM393 binds and inhibits, and the function of these host target genes, as elaborated



hereinbelow.

- [19263] Nucleotide sequences of the VGAM393 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM393 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM393 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM393 are further described hereinbelow with reference to Table 1.
- [19264] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM393 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM393 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19265] As mentioned hereinabove with reference to Fig. 1, a function of VGAM393 gene, herein designated VGAM is inhibition of expression of VGAM393 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM393 correlate with, and may be deduced from, the identity of the target genes which VGAM393 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19266] AS3 (Accession NM\_015928) is a VGAM393 host target gene. AS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AS3 BINDING SITE, designated SEQ ID:18048, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19267] A function of VGAM393 is therefore inhibition of AS3 (Accession NM\_015928), a gene which inhibits cell proliferation. Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AS3. The function of AS3 has been established by previous studies. In the prostate of adult mammals, most epithelial cells are in a state of proliferative quiescence. Androgens regulate this effect by inducing cell cycle arrest in the G0/G1 phase. Geck et al. (2000) identified potential mediators of this androgen-induced proliferative shutoff by means of subtractive cDNA libraries. The expression pattern of one of these sequences, designated AS3, strongly correlated with the expression of the androgen-induced proliferative shutoff

both temporally and dosewise. The AS3 gene is upregulated during androgen-induced proliferative shutoff and induces cell proliferation arrest when expressed in a retrovirus transduced model. The deduced 1,391-amino acid AS3 protein has putative transactivating features, protein-protein interaction motifs (coiled coil and leucine zipper), and DNA-binding domains, suggesting that AS3 is a transcription factor. AS3 also has a protein-kinase motif, suggesting that it may act by phosphorylating a target protein. Geck et al. (1999) demonstrated that the transcript of the AS3 gene has 34 exons spanning approximately 200 kb of genomic DNA. By homology searching in GenBank, they demonstrated that the AS3 gene lies on 13q12-q13, downstream of the breast cancer susceptibility gene BRCA2 (OMIM Ref. No. 600185) and centromeric to the retinoblastoma (RB1; 180200) locus. Geck et al. (2001) presented data on the location of the AS3 gene in relation to BRCA2 and pointed out that the D13S171 marker, which had been widely used as an intra-genic marker of BRCA2, is actually located in the center of the 200-kb AS3 gene. The microsatellite instability of the S171 marker links the AS3 gene to a variety of cancers.

[19268] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [19269] Geck, P.; Sonnenschein, C.; Soto, A. M. : The D13S171 marker, misannotated to BRCA2, links the AS3 gene to various cancers. (Letter) Am. J. Hum. Genet. 69: 461–463, 2001. ; and
- [19270] Geck, P.; Szelei, J.; Jimenez, J.; Sonnenschein, C.; Soto, A. M. : Early gene expression during androgen-induced inhibition of proliferation of prostate cancer cells: a new suppressor.
- [19271] Further studies establishing the function and utilities of AS3 are found in John Hopkins OMIM database record ID 605333, and in cited publications numbered 4791–2307 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Citron (rho-interacting, serine/threonine kinase 21) (CIT, Accession XM\_045786) is another VGAM393 host target gene. CIT BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CIT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CIT BINDING SITE, designated SEQ ID:34561, to the nu-

cleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19272] Another function of VGAM393 is therefore inhibition of Citron (rho-interacting, serine/threonine kinase 21) (CIT, Accession XM\_045786), a gene which is increased several-fold by coexpression of constitutively active Rho . Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CIT. The function of CIT has been established by previous studies. Activated Rho GTPases (see OMIM Ref. No. 602924) trigger distinctive kinase cascades. In particular, ROCK (see OMIM Ref. No. ROCK1, 601702) binds to Rho, and its kinase activity is moderately stimulated by this association. The citron molecule (Madaule et al., 1995), a specific interactor of Rho and Rac (see OMIM Ref. No. 602048), shares a significant degree of structural homology with ROCK; however, its lack of a kinase domain raised the question of its biologic function. By PCR of a mouse primary keratinocyte cDNA library, Di Cunto et al. (1998) identified a novel serine/threonine kinase, CRIK (citron Rho-interacting kinase), belonging to the myotonic dystrophy kinase (see OMIM Ref. No. 605377) family. CRIK can be expressed as at least 2 iso-

forms, one of which encompasses the previously reported form of citron in almost its entirety. The long form of CRIK is a 240-kD protein in which the kinase domain is followed by the sequence of citron. The short form, CRIK-SK (short kinase), is an approximately 54-kD protein that consists mostly of the kinase domain. CRIK and CRIK-SK proteins are capable of phosphorylating exogenous substrates as well as of autophosphorylation, when tested by in vitro kinase assays after expression into COS-7 cells. CRIK kinase activity is increased several-fold by coexpression of constitutively active Rho, while active Rac has more limited effects. Kinase activity of the endogenous CRIK is indicated by in vitro kinase assays after immunoprecipitation with antibodies recognizing the citron moiety of the protein. When expressed in keratinocytes, full-length CRIK, but not CRIK-SK, localizes into corpuscular cytoplasmic structures and elicits recruitment of actin into these structures. The previously reported Rho-associated kinases ROCK1 and ROCK2 (OMIM Ref. No. 604002) are ubiquitously expressed. Northern blot analysis of mouse tissues revealed a restricted pattern of expression limited to keratinocytes, brain, spleen, lung, kidney, and an especially strong signal in testis. No expression was detectable

in heart, liver, or skeletal muscle. The CRIK protein contains a kinase domain, a coiled-coil domain, a leucine-rich domain, a Rho-Rac binding domain, a zinc finger region, a pleckstrin homology domain, and a putative SH3-binding domain. Di Cunto et al. (1998) reported cloning the human homolog of the CRIK kinase domain. They stated that the human homolog of citron is contained within a PAC clone (GenBank AC002563) mapping to chromosome 12q. Animal model experiments lend further support to the function of CIT. Di Cunto et al. (2000) generated mice deficient in citron kinase by targeted disruption. Citron-K  $-/-$  mice grow at slower rates, are severely ataxic, and die before adulthood as a consequence of fatal seizures. Their brains display defective neurogenesis, with dramatic depletion of microneurons in the olfactory bulb, hippocampus, and cerebellum. These abnormalities arise during development of the central nervous system due to altered cytokinesis and massive apoptosis. Di Cunto et al. (2000) concluded that citron-K is essential for cytokinesis in vivo, in specific neuronal precursors only. Moreover, they suggested a novel molecular mechanism for a subset of human malformation syndromes of the central nervous system.

[19273] It is appreciated that the abovementioned animal model for CIT is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[19274] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19275] Di Cunto, F.; Imarisio, S.; Hirsch, E.; Broccoli, V.; Bulfone, A.; Migheli, A.; Atzori, C.; Turco, E.; Triolo, R.; Dotto, G. P.; Silengo, L.; Altruda, F. : Defective neurogenesis in citron kinase knockout mice by altered cytokinesis and massive apoptosis. *Neuron* 28: 115–127, 2000. ; and

[19276] Madaule, P.; Furuyashiki, T.; Reid, T.; Ishizaki, T.; Watanabe, G.; Morii, N.; Narumiya, S. : A novel partner for the GTP-bound forms of rho and rac. *FEBS Lett.* 377: 243–248, 1995.

[19277] Further studies establishing the function and utilities of CIT are found in John Hopkins OMIM database record ID 605629, and in sited publications numbered 6960–696 and 8593 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fragile X Mental Retardation 1 (FMR1, Accession NM\_002024) is another VGAM393 host target gene. FMR1 BINDING SITE is



HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FMR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FMR1 BINDING SITE, designated SEQ ID:7774, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19278] Another function of VGAM393 is therefore inhibition of Fragile X Mental Retardation 1 (FMR1, Accession NM\_002024). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FMR1. Radixin (RDX, Accession NM\_002906) is another VGAM393 host target gene. RDX BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RDX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RDX BINDING SITE, designated SEQ ID:8807, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19279] Another function of VGAM393 is therefore inhibition of

Radixin (RDX, Accession NM\_002906), a gene which plays a crucial role in the binding of the barbed end of actin filaments to the plasma membrane. Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RDX. The function of RDX and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM290. Chromosome 20 Open Reading Frame 130 (C20orf130, Accession XM\_029741) is another VGAM393 host target gene. C20orf130 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C20orf130, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf130 BINDING SITE, designated SEQ ID:30935, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19280] Another function of VGAM393 is therefore inhibition of Chromosome 20 Open Reading Frame 130 (C20orf130, Accession XM\_029741). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with C20orf130. CDK5 Regulatory Subunit Associated Protein 3 (CDK5RAP3, Accession NM\_025197) is another VGAM393 host target gene. CDK5RAP3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CDK5RAP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDK5RAP3 BINDING SITE, designated SEQ ID:24853, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19281] Another function of VGAM393 is therefore inhibition of CDK5 Regulatory Subunit Associated Protein 3 (CDK5RAP3, Accession NM\_025197). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDK5RAP3. CXYorf1 (Accession XM\_088704) is another VGAM393 host target gene. CXYorf1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CXYorf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of CXYorf1 BINDING SITE, designated SEQ ID:39902, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19282] Another function of VGAM393 is therefore inhibition of CXYorf1 (Accession XM\_088704). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CXYorf1. FLJ12704 (Accession NM\_024998) is another VGAM393 host target gene. FLJ12704 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12704, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12704 BINDING SITE, designated SEQ ID:24562, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19283] Another function of VGAM393 is therefore inhibition of FLJ12704 (Accession NM\_024998). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12704. HCA4 (Accession XM\_085287) is another VGAM393 host

target gene. HCA4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HCA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCA4 BINDING SITE, designated SEQ ID:38026, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19284] Another function of VGAM393 is therefore inhibition of HCA4 (Accession XM\_085287). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCA4. KIAA0427 (Accession NM\_014772) is another VGAM393 host target gene. KIAA0427 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0427, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0427 BINDING SITE, designated SEQ ID:16576, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19285] Another function of VGAM393 is therefore inhibition of KIAA0427 (Accession NM\_014772). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0427. MSTP028 (Accession NM\_031954) is another VGAM393 host target gene. MSTP028 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSTP028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSTP028 BINDING SITE, designated SEQ ID:25695, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19286] Another function of VGAM393 is therefore inhibition of MSTP028 (Accession NM\_031954). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSTP028. LOC120939 (Accession XM\_073688) is another VGAM393 host target gene. LOC120939 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC120939, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120939 BINDING SITE, designated SEQ ID:37514, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19287] Another function of VGAM393 is therefore inhibition of LOC120939 (Accession XM\_073688). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120939. LOC149301 (Accession XM\_086480) is another VGAM393 host target gene. LOC149301 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149301 BINDING SITE, designated SEQ ID:38688, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19288] Another function of VGAM393 is therefore inhibition of LOC149301 (Accession XM\_086480). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC149301. LOC152274 (Accession XM\_087418) is another VGAM393 host target gene. LOC152274 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152274, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152274 BINDING SITE, designated SEQ ID:39229, to the nucleotide sequence of VGAM393 RNA, herein designated VGAM RNA, also designated SEQ ID:3104.

[19289] Another function of VGAM393 is therefore inhibition of LOC152274 (Accession XM\_087418). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152274. LOC200093 (Accession XM\_032184) is another VGAM393 host target gene. LOC200093 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200093, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200093 BINDING SITE, designated SEQ ID:31594, to the nucleotide sequence of VGAM393 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3104.

[19290] Another function of VGAM393 is therefore inhibition of LOC200093 (Accession XM\_032184). Accordingly, utilities of VGAM393 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200093. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 394 (VGAM394) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19291] VGAM394 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM394 was detected is described hereinabove with reference to Figs. 1–8.

[19292] VGAM394 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM394 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19293] VGAM394 gene encodes a VGAM394 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM394 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM394 precursor RNA is designated SEQ ID:380, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:380 is located at position 4060 relative to the genome of Cryphonectria Hypovirus 1.

[19294] VGAM394 precursor RNA folds onto itself, forming VGAM394 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19295] An enzyme complex designated DICER COMPLEX, `dices` the VGAM394 folded precursor RNA into VGAM394 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM394 RNA is designated SEQ ID:3105, and is provided hereinbelow with reference to the sequence listing part.

[19296] VGAM394 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM394 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM394 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19297] VGAM394 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM394 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM394 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM394 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM394 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19298] The complementary binding of VGAM394 RNA, herein designated VGAM RNA, to host target binding sites on VGAM394 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM394 host target RNA into VGAM394 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19299] It is appreciated that VGAM394 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM394 host target genes. The mRNA of

each one of this plurality of VGAM394 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM394 RNA, herein designated VGAM RNA, and which when bound by VGAM394 RNA causes inhibition of translation of respective one or more VGAM394 host target proteins.

[19300] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM394 gene, herein designated VGAM GENE, on one or more VGAM394 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[19301] It is yet further appreciated that a function of VGAM394 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM394 correlate with, and may be deduced from, the identity of the host target genes which VGAM394 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19302] Nucleotide sequences of the VGAM394 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM394 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM394 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM394 are further described hereinbelow with reference to Table 1.

[19303] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM394 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM394 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[19304] As mentioned hereinabove with reference to Fig. 1, a function of VGAM394 gene, herein designated VGAM is inhibition of expression of VGAM394 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM394 correlate with, and may be deduced from, the identity of the target genes which VGAM394 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19305] Aryl-hydrocarbon Receptor Nuclear Translocator 2 (ARNT2, Accession NM\_014862) is a VGAM394 host target gene. ARNT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARNT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARNT2 BINDING SITE, designated SEQ ID:16935, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19306] A function of VGAM394 is therefore inhibition of Aryl-hydrocarbon Receptor Nuclear Translocator 2 (ARNT2, Ac-

cession NM\_014862), a gene which specifically recognizes the xenobiotic response element (xre). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARNT2. The function of ARNT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM345. CRACC (Accession NM\_021181) is another VGAM394 host target gene. CRACC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRACC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRACC BINDING SITE, designated SEQ ID:22155, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19307] Another function of VGAM394 is therefore inhibition of CRACC (Accession NM\_021181), a gene which may participate in adhesion reactions between T lymphocytes and accessory cells. Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRACC. The function of



CRACC and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM26. DNA Fragmentation Factor, 40kDa, Beta Polypeptide (caspase-activated DNase) (DFFB, Accession XM\_113366) is another VGAM394 host target gene. DFFB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DFFB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DFFB BINDING SITE, designated SEQ ID:42241, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19308] Another function of VGAM394 is therefore inhibition of DNA Fragmentation Factor, 40kDa, Beta Polypeptide (caspase-activated DNase) (DFFB, Accession XM\_113366), a gene which induces DNA fragmentation and chromatin condensation during apoptosis. Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DFFB. The function of DFFB and its association with various diseases and clinical conditions, has been established by previous

studies, as described hereinabove with reference to VGAM74. Glucose-6-phosphatase, Transport (glucose-6-phosphate) Protein 1 (G6PT1, Accession NM\_001467) is another VGAM394 host target gene. G6PT1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by G6PT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of G6PT1 BINDING SITE, designated SEQ ID:7201, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19309] Another function of VGAM394 is therefore inhibition of Glucose-6-phosphatase, Transport (glucose-6-phosphate) Protein 1 (G6PT1, Accession NM\_001467). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with G6PT1. Huntingtin (Huntington disease) (HD, Accession NM\_002111) is another VGAM394 host target gene. HD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HD BINDING SITE, designated SEQ ID:7894, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19310] Another function of VGAM394 is therefore inhibition of Huntingtin (Huntington disease) (HD, Accession NM\_002111). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HD. Vinculin (VCL, Accession NM\_003373) is another VGAM394 host target gene. VCL BINDING SITE1 and VCL BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by VCL, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VCL BINDING SITE1 and VCL BINDING SITE2, designated SEQ ID:9407 and SEQ ID:15196 respectively, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19311] Another function of VGAM394 is therefore inhibition of Vinculin (VCL, Accession NM\_003373). Accordingly, utili-

ties of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VCL. FLJ10815 (Accession NM\_018231) is another VGAM394 host target gene. FLJ10815 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10815, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10815 BINDING SITE, designated SEQ ID:20171, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19312] Another function of VGAM394 is therefore inhibition of FLJ10815 (Accession NM\_018231). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10815. FLJ20320 (Accession NM\_017765) is another VGAM394 host target gene. FLJ20320 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20320, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20320 BINDING SITE,

designated SEQ ID:19382, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19313] Another function of VGAM394 is therefore inhibition of FLJ20320 (Accession NM\_017765). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20320. FLJ23191 (Accession NM\_024574) is another VGAM394 host target gene. FLJ23191 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ23191, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23191 BINDING SITE, designated SEQ ID:23802, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19314] Another function of VGAM394 is therefore inhibition of FLJ23191 (Accession NM\_024574). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23191. KIAA0449 (Accession NM\_017596) is another VGAM394 host target gene. KIAA0449 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by KIAA0449, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0449 BINDING SITE, designated SEQ ID:19050, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19315] Another function of VGAM394 is therefore inhibition of KIAA0449 (Accession NM\_017596). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0449. TIP47 (Accession NM\_005817) is another VGAM394 host target gene. TIP47 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIP47, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIP47 BINDING SITE, designated SEQ ID:12417, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19316] Another function of VGAM394 is therefore inhibition of

TIP47 (Accession NM\_005817). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIP47.

LOC145757 (Accession XM\_085227) is another VGAM394 host target gene. LOC145757 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145757, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145757 BINDING SITE, designated SEQ ID:37969, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19317] Another function of VGAM394 is therefore inhibition of LOC145757 (Accession XM\_085227). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145757. LOC146481 (Accession XM\_085484) is another VGAM394 host target gene. LOC146481 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146481, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC146481 BINDING SITE, designated SEQ ID:38176, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19318] Another function of VGAM394 is therefore inhibition of LOC146481 (Accession XM\_085484). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146481. LOC90333 (Accession XM\_030958) is another VGAM394 host target gene. LOC90333 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90333 BINDING SITE, designated SEQ ID:31224, to the nucleotide sequence of VGAM394 RNA, herein designated VGAM RNA, also designated SEQ ID:3105.

[19319] Another function of VGAM394 is therefore inhibition of LOC90333 (Accession XM\_030958). Accordingly, utilities of VGAM394 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90333. Fig. 1 further provides a conceptual descrip-



tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 395 (VGAM395) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19320] VGAM395 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM395 was detected is described hereinabove with reference to Figs. 1–8.

[19321] VGAM395 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM395 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19322] VGAM395 gene encodes a VGAM395 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM395 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM395 precursor RNA is designated SEQ ID:381, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:381 is

located at position 9833 relative to the genome of Cryphonectria Hypovirus 1.

[19323] VGAM395 precursor RNA folds onto itself, forming VGAM395 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19324] An enzyme complex designated DICER COMPLEX, `dices` the VGAM395 folded precursor RNA into VGAM395 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 48%) nucleotide sequence of VGAM395 RNA is designated SEQ ID:3106, and is provided hereinbelow with reference to the sequence listing part.

[19325] VGAM395 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM395 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM395 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[19326] VGAM395 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM395 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM395 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM395 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM395 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[19327] The complementary binding of VGAM395 RNA, herein designated VGAM RNA, to host target binding sites on VGAM395 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM395 host target RNA into VGAM395 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19328] It is appreciated that VGAM395 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM395 host target genes. The mRNA of each one of this plurality of VGAM395 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM395 RNA, herein designated VGAM RNA, and which when bound by VGAM395 RNA causes inhibition of translation of respective one or more VGAM395

host target proteins.

[19329] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM395 gene, herein designated VGAM GENE, on one or more VGAM395 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19330] It is yet further appreciated that a function of VGAM395 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM395 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1.

Specific functions, and accordingly utilities, of VGAM395 correlate with, and may be deduced from, the identity of the host target genes which VGAM395 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [19331] Nucleotide sequences of the VGAM395 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM395 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM395 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM395 are further described hereinbelow with reference to Table 1.
- [19332] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM395 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM395 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19333] As mentioned hereinabove with reference to Fig. 1, a function of VGAM395 gene, herein designated VGAM is inhibition of expression of VGAM395 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM395 correlate with, and may be deduced from, the identity of the target genes which VGAM395 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19334] G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_014776) is a VGAM395 host target gene. GIT2 BINDING SITE1 through GIT2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GIT2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GIT2 BINDING SITE1 through GIT2 BINDING SITE3, designated SEQ ID:16606, SEQ ID:27688 and SEQ ID:27701 respectively, to the nucleotide sequence of VGAM395 RNA, herein designated VGAM RNA, also designated SEQ ID:3106.

[19335] A function of VGAM395 is therefore inhibition of G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_014776). Accordingly, utilities of VGAM395 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GIT2. Zinc Finger Protein 36, C3H Type-like 2 (ZFP36L2, Accession NM\_006887) is another VGAM395 host target gene.

ZFP36L2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZFP36L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFP36L2 BINDING SITE, designated SEQ ID:13752, to the nucleotide sequence of VGAM395 RNA, herein designated VGAM RNA, also designated SEQ ID:3106.

[19336] Another function of VGAM395 is therefore inhibition of Zinc Finger Protein 36, C3H Type-like 2 (ZFP36L2, Accession NM\_006887). Accordingly, utilities of VGAM395 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFP36L2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 396 (VGAM396) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19337] VGAM396 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM396 was detected is described



hereinabove with reference to Figs. 1–8.

[19338] VGAM396 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM396 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19339] VGAM396 gene encodes a VGAM396 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM396 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM396 precursor RNA is designated SEQ ID:382, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:382 is located at position 2659 relative to the genome of Cryphonectria Hypovirus 1.

[19340] VGAM396 precursor RNA folds onto itself, forming VGAM396 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19341] An enzyme complex designated DICER COMPLEX, `dices` the VGAM396 folded precursor RNA into VGAM396 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM396 RNA is designated SEQ ID:3107, and is provided hereinbelow with reference to the sequence listing part.

[19342] VGAM396 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM396 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM396 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19343] VGAM396 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM396 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM396 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM396 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM396 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19344] The complementary binding of VGAM396 RNA, herein designated VGAM RNA, to host target binding sites on VGAM396 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM396 host target RNA into VGAM396 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19345] It is appreciated that VGAM396 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM396 host target genes. The mRNA of each one of this plurality of VGAM396 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM396 RNA, herein designated VGAM RNA, and which when bound by VGAM396 RNA causes inhibition of translation of respective one or more VGAM396 host target proteins.

[19346] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM396 gene, herein designated VGAM GENE, on one or more VGAM396 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19347] It is yet further appreciated that a function of VGAM396 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM396 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM396 correlate with, and may be deduced from, the identity of the host target genes which VGAM396 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19348] Nucleotide sequences of the VGAM396 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM396 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM396 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM396 are further described hereinbelow with reference to Table 1.

[19349] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM396 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM396 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19350] As mentioned hereinabove with reference to Fig. 1, a function of VGAM396 gene, herein designated VGAM is inhibition of expression of VGAM396 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM396 correlate with, and may be deduced from, the identity of the target genes which VGAM396 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19351] Thy-1 Cell Surface Antigen (THY1, Accession NM\_006288) is a VGAM396 host target gene. THY1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by THY1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of THY1 BINDING SITE, designated SEQ ID:12975, to the nucleotide sequence of VGAM396 RNA, herein designated VGAM RNA, also designated SEQ ID:3107.

[19352] A function of VGAM396 is therefore inhibition of Thy-1 Cell Surface Antigen (THY1, Accession NM\_006288), a gene which plays a role in cell-cell or cell-ligand interactions during synaptogenesis. Accordingly, utilities of VGAM396 include diagnosis, prevention and treatment of diseases and clinical conditions associated with THY1. The function of THY1 has been established by previous studies. Thy-1 is the designation for a major cell surface glycoprotein characteristic to T cells, as first defined in the mouse and rat (Raff, 1971; Letarte-Muirhead et al., 1975). The Thy-1 glycoproteins are constituents of thymocytes and neurons and probably are involved in cell-cell interactions. The putative human homolog of Thy-1 of the mouse is called K117. The human homolog of the rodent antigen was studied by Ades et al. (1980). Using a monoclonal antibody, McKenzie and Fabre (1981) studied the tissue distribution of the antigen. By use of a gene clone in somatic cell hybrids, Seki et al. (1985) assigned the

THY1 gene to chromosome 11. Van den Elsen et al. (1985) predicted that the human Thy-1 homolog maps to chromosome 11 because that is where they found T3D (OMIM Ref. No. 186790) to map and in the mouse T3D and Thy-1 map to chromosome 9 along with certain other loci that are on human 11q. A multigene family is a group of homologous genes with similar function. A supergene family is a set of multigene families and single genes related by sequence (implying common ancestry) but not necessarily related in function. Hood et al. (1985) refer to the immunoglobulin supergene family which includes Thy-1, poly-Ig receptor, heavy, kappa and lambda immunoglobulins, Lyt-2 (T8), alpha and beta chains of T-cell antigen receptor and the closely homologous gamma chain, class I MHC antigen, beta-2-microglobulin, and the alpha and beta chains of class II MHC antigens. Thy-1 is structurally the simplest of these, consisting of a single immunoglobulin homology unit that is either intermediate between V and C or somewhat more similar to a V homology unit (Williams and Gagnon, 1982). The Thy-1 glycoprotein is also exceptional in that it is on the cell surface as a free homology unit and apparently does not associate either with itself or with other polypeptides. Its role in immune



response is unclear. It is expressed on fibroblasts and brain cells in addition to some T cells. The significant role of Thy-1 in developing nervous tissue (Morris, 1985) may be of relevance to disorders such as ataxia-telangiectasia (OMIM Ref. No. 208900) that combine neurologic and immunologic defects. By somatic cell and in situ hybridization, van Rijs et al. (1985) localized the gene to 11q23-11q24. Rettig et al. (1985) assigned the gene to 11q13-qter, by Southern analysis of DNA from hybrid cells containing rearranged chromosomes 11. HGM7 gave the regional assignment as 11q22.3. Tunnacliffe and McGuire (1990) constructed a physical map of 11q23 by pulsed field gel electrophoresis and showed that THY1 lies in 11q23.3 as the most telomeric of a group of 6 genes: cen--CD3E--CD3D--CD3G--PBGD--CBL2--THY1--qter. Greenspan and O'Brien (1989) showed in the mouse that a factor secreted by nonneuronal accessory cells of dorsal root ganglion cultures stimulates neurite outgrowth in neonatal sympathetic ganglion neurons. They presented evidence that this is identical to Thy-1. It is this function in separate tissues that might explain pleiotropic manifestations of some syndromes such as ataxia-telangiectasia (OMIM Ref. No. 208900) or cartilage-hair

hypoplasia (OMIM Ref. No. 250250).

[19353] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19354] Morris, R. : Thy-1 in developing nervous tissue. Dev. Neurosci. 7: 133-160, 1985. ; and

[19355] Greenspan, R. J.; O'Brien, M. C. : Genetic evidence for the role of Thy-1 in neurite outgrowth in the mouse. J. Neurogenet. 5: 25-36, 1989.

[19356] Further studies establishing the function and utilities of THY1 are found in John Hopkins OMIM database record ID 188230, and in cited publications numbered 9685-9690, 10262-9700, 88 and 10082-10084 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZp547I224 (Accession NM\_020221) is another VGAM396 host target gene. DKFZp547I224 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp547I224, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547I224 BINDING SITE, designated SEQ ID:21471, to the nucleotide sequence of

VGAM396 RNA, herein designated VGAM RNA, also designated SEQ ID:3107.

[19357] Another function of VGAM396 is therefore inhibition of DKFZp547I224 (Accession NM\_020221). Accordingly, utilities of VGAM396 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547I224. GTP Binding Protein 5 (putative) (GTPBP5, Accession XM\_037206) is another VGAM396 host target gene. GTPBP5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GTPBP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GTPBP5 BINDING SITE, designated SEQ ID:32576, to the nucleotide sequence of VGAM396 RNA, herein designated VGAM RNA, also designated SEQ ID:3107.

[19358] Another function of VGAM396 is therefore inhibition of GTP Binding Protein 5 (putative) (GTPBP5, Accession XM\_037206). Accordingly, utilities of VGAM396 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GTPBP5. LOC145845 (Accession XM\_096884) is another VGAM396 host target

gene. LOC145845 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145845, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145845 BINDING SITE, designated SEQ ID:40615, to the nucleotide sequence of VGAM396 RNA, herein designated VGAM RNA, also designated SEQ ID:3107.

[19359] Another function of VGAM396 is therefore inhibition of LOC145845 (Accession XM\_096884). Accordingly, utilities of VGAM396 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145845. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 397 (VGAM397) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19360] VGAM397 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM397 was detected is described

hereinabove with reference to Figs. 1–8.

[19361] VGAM397 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM397 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19362] VGAM397 gene encodes a VGAM397 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM397 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM397 precursor RNA is designated SEQ ID:383, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:383 is located at position 5663 relative to the genome of Cryphonectria Hypovirus 1.

[19363] VGAM397 precursor RNA folds onto itself, forming VGAM397 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[19364] An enzyme complex designated DICER COMPLEX, `dices` the VGAM397 folded precursor RNA into VGAM397 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 57%) nucleotide sequence of VGAM397 RNA is designated SEQ ID:3108, and is provided hereinbelow with reference to the sequence listing part.

[19365] VGAM397 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM397 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM397 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19366] VGAM397 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM397 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM397 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM397 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM397 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19367] The complementary binding of VGAM397 RNA, herein designated VGAM RNA, to host target binding sites on VGAM397 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM397 host target RNA into VGAM397 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19368] It is appreciated that VGAM397 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM397 host target genes. The mRNA of each one of this plurality of VGAM397 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM397 RNA, herein designated VGAM RNA, and which when bound by VGAM397 RNA causes inhibition of translation of respective one or more VGAM397 host target proteins.

[19369] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM397 gene, herein designated VGAM GENE, on one or more VGAM397 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-



cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19370] It is yet further appreciated that a function of VGAM397 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM397 correlate with, and may be deduced from, the identity of the host target genes which VGAM397 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19371] Nucleotide sequences of the VGAM397 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM397 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM397 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM397 are further described hereinbelow with reference to Table 1.

[19372] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM397 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM397 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19373] As mentioned hereinabove with reference to Fig. 1, a function of VGAM397 gene, herein designated VGAM is inhibition of expression of VGAM397 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM397 correlate with, and may be deduced from, the identity of the target genes which VGAM397 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19374] Solute Carrier Family 22 (organic cation transporter), Member 1-like Antisense (SLC22A1LS, Accession NM\_007105) is a VGAM397 host target gene. SLC22A1LS BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SLC22A1LS,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC22A1LS BINDING SITE, designated SEQ ID:13962, to the nucleotide sequence of VGAM397 RNA, herein designated VGAM RNA, also designated SEQ ID:3108.

[19375] A function of VGAM397 is therefore inhibition of Solute Carrier Family 22 (organic cation transporter), Member 1-like Antisense (SLC22A1LS, Accession NM\_007105), a gene which may function in the regulation of the ORCTL2 gene. Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC22A1LS. The function of SLC22A1LS has been established by previous studies. Human chromosomal band 11p15.5 has been shown to contain genes involved in the development of several pediatric and adult tumors and in Beckwith-Wiedemann syndrome (BWS; 130650). Several genes in this region, including IGF2 (OMIM Ref. No. 147470), H19 (OMIM Ref. No. 103280), CDKN1C (OMIM Ref. No. 600856), IPL (TSSC3; 602131), and KVLQT1 (OMIM Ref. No. 192500), are known to undergo genomic imprinting. By genomic sequencing

of overlapping PAC clones from 11p15.5, followed by the identification of matching ESTs, Cooper et al. (1998) identified the organic-cation transporter-like-2 (ORCTL2; 602631) and ORCTL2-antisense (ORCTL2S) (GenBank AF037066) genes. Northern blot analysis indicated that these genes are predominantly expressed in fetal and adult liver and kidney. The ORCTL2 and ORCTL2S genes overlap in their 5-prime regions in divergent orientations, with the first exon of ORCTL2S sharing 31 bp with the second exon of ORCTL2. The ORCTL2S gene contains 4 exons spread over approximately 12 kb. It may have multiple transcription start sites or promoters. The largest open reading frame within the full-length ORCTL2S cDNA isolated by the authors encodes a putative 253-amino acid protein. Since ORCTL2S showed no significant similarity to DNA or protein sequences in the databases and lacks good matches to the Kozak and polyadenylation consensus sequences, Cooper et al. (1998) suggested that the ORCTL2S gene may not be translated and may function in the regulation of the ORCTL2 gene. The authors were unable to determine if the ORCTL2S gene is imprinted. They did not detect disease-associated mutations in the ORCTL2S genes of 62 Wilms tumor (WT; 194071)

patients or 10 BWS patients By genomic analysis of a 170-kb region at 11p15.5 between loci D11S601 and D11S679, Schwienbacher et al. (1998) identified 6 genes: NAP2 (OMIM Ref. No. 601651), CDKN1C, KVLQT1, BWR1A (ORCTL2, or SLC22A1L), BWR1B, and BWR1C (TSSC3), with BWR designating 'Beckwith–Wiedemann region.' Schwienbacher et al. (1998) cloned the full-length BWR1B cDNA from a human fetal liver cDNA library. The open reading frame encoded a protein of 253 amino acids with no significant homology to known proteins or motifs. Northern blot analysis revealed that the gene is expressed as a 1.2– to 1.3-kb mRNA most abundant in gastrointestinal tissues, but also detectable in kidney and placenta.

[19376] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [19377] Cooper, P. R.; Smilnich, N. J.; Day, C. D.; Nowak, N. J.; Reid, L. H.; Pearsall, R. S.; Reece, M.; Prawitt, D.; Landers, J.; Housman, D. E.; Winterpacht, A.; Zabel, B. U.; Pelletier, J.; Weissman, B. E.; Shows, T. B.; Higgins, M. J. : Divergently transcribed overlapping genes expressed in liver and kidney and located in the 11p15.5 imprinted domain. *Genomics* 49: 38–51, 1998. ; and
- [19378] Schwienbacher, C.; Sabbioni, S.; Campi, M.; Veronese, A.; Bernardi, G.; Menegatti, A.; Hatada, I.; Mukai, T.; Ohashi, H.; Barbanti-Brodano, G; Croce, C. M.; Negrini, M. : Transcriptional ma.
- [19379] Further studies establishing the function and utilities of SLC22A1LS are found in John Hopkins OMIM database record ID 603240, and in cited publications numbered 8748 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Rho/rac Guanine Nucleotide Exchange Factor (GEF) 2 (ARHGEF2, Accession NM\_004723) is another VGAM397 host target gene. ARHGEF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGEF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of ARHGEF2 BINDING SITE, designated SEQ ID:11091, to the nucleotide sequence of VGAM397 RNA, herein designated VGAM RNA, also designated SEQ ID:3108.

[19380] Another function of VGAM397 is therefore inhibition of Rho/rac Guanine Nucleotide Exchange Factor (GEF) 2 (ARHGEF2, Accession NM\_004723). Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGEF2. FLJ12681 (Accession NM\_022773) is another VGAM397 host target gene. FLJ12681 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12681, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12681 BINDING SITE, designated SEQ ID:23035, to the nucleotide sequence of VGAM397 RNA, herein designated VGAM RNA, also designated SEQ ID:3108.

[19381] Another function of VGAM397 is therefore inhibition of FLJ12681 (Accession NM\_022773). Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12681.

FLJ30213 (Accession NM\_145008) is another VGAM397 host target gene. FLJ30213 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ30213, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ30213 BINDING SITE, designated SEQ ID:29608, to the nucleotide sequence of VGAM397 RNA, herein designated VGAM RNA, also designated SEQ ID:3108.

[19382] Another function of VGAM397 is therefore inhibition of FLJ30213 (Accession NM\_145008). Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ30213. LOC153688 (Accession XM\_098416) is another VGAM397 host target gene. LOC153688 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153688, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153688 BINDING SITE, designated SEQ ID:41651, to the nucleotide sequence of VGAM397 RNA, herein designated VGAM RNA,



also designated SEQ ID:3108.

[19383] Another function of VGAM397 is therefore inhibition of LOC153688 (Accession XM\_098416). Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153688. LOC222066 (Accession XM\_166582) is another VGAM397 host target gene. LOC222066 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222066, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222066 BINDING SITE, designated SEQ ID:44552, to the nucleotide sequence of VGAM397 RNA, herein designated VGAM RNA, also designated SEQ ID:3108.

[19384] Another function of VGAM397 is therefore inhibition of LOC222066 (Accession XM\_166582). Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222066. LOC91464 (Accession XM\_038589) is another VGAM397 host target gene. LOC91464 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91464, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91464 BINDING SITE, designated SEQ ID:32871, to the nucleotide sequence of VGAM397 RNA, herein designated VGAM RNA, also designated SEQ ID:3108.

[19385] Another function of VGAM397 is therefore inhibition of LOC91464 (Accession XM\_038589). Accordingly, utilities of VGAM397 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91464. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 398 (VGAM398) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19386] VGAM398 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM398 was detected is described hereinabove with reference to Figs. 1–8.

[19387] VGAM398 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus

1. VGAM398 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19388] VGAM398 gene encodes a VGAM398 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM398 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM398 precursor RNA is designated SEQ ID:384, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:384 is located at position 5176 relative to the genome of Cryphonectria Hypovirus 1.

[19389] VGAM398 precursor RNA folds onto itself, forming VGAM398 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19390] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM398 folded precursor RNA into VGAM398 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM398 RNA is designated SEQ ID:3109, and is provided hereinbelow with reference to the sequence listing part.

[19391] VGAM398 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM398 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM398 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19392] VGAM398 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM398 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM398 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM398 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM398 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19393] The complementary binding of VGAM398 RNA, herein designated VGAM RNA, to host target binding sites on VGAM398 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM398 host target RNA into VGAM398 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19394] It is appreciated that VGAM398 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM398 host target genes. The mRNA of each one of this plurality of VGAM398 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM398 RNA, herein designated VGAM RNA, and which when bound by VGAM398 RNA causes inhibition of translation of respective one or more VGAM398 host target proteins.

[19395] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM398 gene, herein designated VGAM GENE, on one or more VGAM398 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19396] It is yet further appreciated that a function of VGAM398 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM398 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM398 correlate with, and may be deduced from, the identity of the host target genes which VGAM398 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19397] Nucleotide sequences of the VGAM398 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM398 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM398 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM398 are further described hereinbelow with reference to Table 1.

[19398] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM398 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM398 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19399] As mentioned hereinabove with reference to Fig. 1, a function of VGAM398 gene, herein designated VGAM is inhibition of expression of VGAM398 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM398 correlate with, and may be deduced from, the identity of the target genes which VGAM398 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19400] Cytochrome P450, Subfamily 46 (cholesterol 24-hydroxylase) (CYP46, Accession NM\_006668) is a VGAM398 host target gene. CYP46 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP46, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP46 BINDING SITE,



designated SEQ ID:13483, to the nucleotide sequence of VGAM398 RNA, herein designated VGAM RNA, also designated SEQ ID:3109.

[19401] A function of VGAM398 is therefore inhibition of Cytochrome P450, Subfamily 46 (cholesterol 24-hydroxylase) (CYP46, Accession NM\_006668). Accordingly, utilities of VGAM398 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP46. RalA Binding Protein 1 (RALBP1, Accession NM\_006788) is another VGAM398 host target gene. RALBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RALBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RALBP1 BINDING SITE, designated SEQ ID:13663, to the nucleotide sequence of VGAM398 RNA, herein designated VGAM RNA, also designated SEQ ID:3109.

[19402] Another function of VGAM398 is therefore inhibition of RalA Binding Protein 1 (RALBP1, Accession NM\_006788), a gene which plays a role in signal transduction and catalyzes the transport of glutathione conjugates and xeno-

biotics. Accordingly, utilities of VGAM398 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RALBP1. The function of RALBP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM345. Chromosome 22 Open Reading Frame 19 (C22orf19, Accession NM\_003678) is another VGAM398 host target gene. C22orf19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C22orf19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C22orf19 BINDING SITE, designated SEQ ID:9775, to the nucleotide sequence of VGAM398 RNA, herein designated VGAM RNA, also designated SEQ ID:3109.

[19403] Another function of VGAM398 is therefore inhibition of Chromosome 22 Open Reading Frame 19 (C22orf19, Accession NM\_003678). Accordingly, utilities of VGAM398 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C22orf19. Fig. 1 further provides a conceptual description of a novel bioin-

formatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 399 (VGAM399) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19404] VGAM399 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM399 was detected is described hereinabove with reference to Figs. 1–8.

[19405] VGAM399 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM399 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19406] VGAM399 gene encodes a VGAM399 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM399 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM399 precursor RNA is designated SEQ ID:385, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:385 is located at position 2559 relative to the genome of Cry–

phonectria Hypovirus 1.

[19407] VGAM399 precursor RNA folds onto itself, forming VGAM399 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19408] An enzyme complex designated DICER COMPLEX, `dices` the VGAM399 folded precursor RNA into VGAM399 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM399 RNA is designated SEQ ID:3110, and is provided hereinbelow with reference to the sequence listing part.

[19409] VGAM399 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM399 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM399 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19410] VGAM399 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM399 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM399 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM399 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM399 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19411] The complementary binding of VGAM399 RNA, herein designated VGAM RNA, to host target binding sites on VGAM399 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM399 host target RNA into VGAM399 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19412] It is appreciated that VGAM399 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM399 host target genes. The mRNA of each one of this plurality of VGAM399 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM399 RNA, herein designated VGAM RNA, and which when bound by VGAM399 RNA causes inhibition of translation of respective one or more VGAM399 host target proteins.

[19413] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM399 gene, herein designated VGAM GENE, on one or more VGAM399 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19414] It is yet further appreciated that a function of VGAM399 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM399

correlate with, and may be deduced from, the identity of the host target genes which VGAM399 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19415] Nucleotide sequences of the VGAM399 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM399 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM399 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM399 are further described hereinbelow with reference to Table 1.

[19416] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM399 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM399 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19417] As mentioned hereinabove with reference to Fig. 1, a function of VGAM399 gene, herein designated VGAM is inhibition of expression of VGAM399 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM399 correlate with, and may be deduced



from, the identity of the target genes which VGAM399 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19418] Deleted In Azoospermia-like (DAZL, Accession XM\_042839) is a VGAM399 host target gene. DAZL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DAZL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAZL BINDING SITE, designated SEQ ID:33802, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19419] A function of VGAM399 is therefore inhibition of Deleted In Azoospermia-like (DAZL, Accession XM\_042839), a gene which may be essential for gametogenesis. Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAZL. The function of DAZL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM206. Exonuclease 1 (EXO1, Accession NM\_130398) is another VGAM399 host target gene.

EXO1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EXO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EXO1 BINDING SITE, designated SEQ ID:28181, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19420] Another function of VGAM399 is therefore inhibition of Exonuclease 1 (EXO1, Accession NM\_130398), a gene which excise and replace mismatched segments. Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EXO1. The function of EXO1 has been established by previous studies. Mutation rates in normal cells are low due to the existence of DNA repair systems in which exonucleases, endonucleases, and helicases excise and replace mismatched segments. By searching an EST database for homologs of the yeast Exo1 gene, Wilson et al. (1998) identified a cDNA encoding human EXO1, which they termed HEX1. Sequence analysis predicted that the 803-amino acid human protein, which is 26% identical to the yeast protein, contains 2 potential nuclear localization

signals, one in its central region and the other in its C-terminal region. Functional analysis indicated that EXO1 has exonuclease activity with a 5-prime-to-3-prime polarity. Northern blot analysis revealed high expression of an approximately 4.0-kb transcript in fetal liver and adult bone marrow, with low levels in other tissues, suggesting that EXO1 may function prominently in DNA metabolic processes occurring during stem cell differentiation.

Schmutte et al. (1998) cloned EXO1, which they predicted encodes an 846-amino acid protein. GST pull-down analysis determined that EXO1 interacts with MSH2 (OMIM Ref. No. 120435), which is involved in susceptibility to familial nonpolyposis colon cancer. Tishkoff et al. (1998) cloned EXO1 and showed that it encodes 2 splice variants, EXO1A and EXO1B, that share the first 802 residues and have C-terminal extensions of 1 and 44 amino acids, respectively. Northern blot analysis detected wide expression of a 3.0-kb transcript, with significantly higher expression in testis, and elevated expression in thymus, colon, and placenta. By FISH, Wilson et al. (1998) mapped the EXO1 gene to 1q42-q43.

[19421] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [19422] Wilson, D. M., III; Carney, J. P.; Coleman, M. A.; Adamson, A. W.; Christensen, M.; Lamerdin, J. E. : Hex1: a new human Rad2 nuclease family member with homology to yeast exonuclease 1. *Nucleic Acids Res.* 26: 3762–3768, 1998. ; and
- [19423] Tishkoff, D. X.; Amin, N. S.; Viars, C. S.; Arden, K. C.; Kolodner, R. D. : Identification of a human gene encoding a homologue of *Saccharomyces cerevisiae* EXO1, an exonuclease implicate.
- [19424] Further studies establishing the function and utilities of EXO1 are found in John Hopkins OMIM database record ID 606063, and in cited publications numbered 6903–6906 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Folate Receptor 1 (adult) (FOLR1, Accession NM\_016730) is another VGAM399 host target gene. FOLR1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FOLR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOLR1 BINDING SITE, designated SEQ ID:18782, to the nucleotide sequence of

VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19425] Another function of VGAM399 is therefore inhibition of Folate Receptor 1 (adult) (FOLR1, Accession NM\_016730), a gene which binds and initiates transport of folate and methotrexate. Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOLR1. The function of FOLR1 has been established by previous studies. To identify cellular entry factors employed by the Marburg (MBG) virus, Chan et al. (2001) used noninfectible cells transfected with an expression library and challenged them with a selectable pseudotype virus packaged by MBG glycoproteins. A cDNA encoding FOLR1 was recovered from cells exhibiting reconstitution of viral entry. A FOLR1 cDNA was also recovered in a similar strategy employing Ebola (EBO) pseudotypes. FOLR1 expression in Jurkat cells facilitated MBG or EBO entry, and FR-blocking reagents inhibited infection by MBG or EBO. Finally, FOLR1 bound cells expressing MBG or EBO glycoproteins and mediated syncytia formation triggered by MBG glycoproteins. The authors concluded that FOLR1 is a significant cofactor for cellular entry for MBG and EBO viruses. Animal model ex-

periments lend further support to the function of FOLR1. Periconceptional folic acid supplementation reduces the occurrence of several human congenital malformations, including craniofacial, heart, and neural tube defects (Czeizel and Dudas, 1992; Werler et al., 1993; Shaw et al., 1994). Although the underlying mechanism is unknown, there may be a maternal-to-fetal folate transport defect or an inherent fetal biochemical disorder that is neutralized by supplementation. To determine whether folic acid-binding protein-1 is involved in maternal-to-fetal folate transport, Piedrahita et al. (1999) inactivated the gene (symbolized *Folbp1* in that species) in mice. They also produced mice lacking *Folbp2* (FOLR2; 136425), another member of the folate receptor family that is GPI-anchored but binds folate poorly. *Folbp2*  $-/-$  embryos developed normally, but *Folbp1*  $-/-$  embryos had severe morphogenetic abnormalities and died in utero by embryonic day 10. Supplementing pregnant *Folbp1*  $+/-$  dams with folic acid reversed this phenotype in nullizygous pups. The results suggested that *Folbp1* has a critical role in folate homeostasis during development, and that functional defects in the human homolog, FOLR1, may contribute to similar defects in humans.

[19426] It is appreciated that the abovementioned animal model for FOLR1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[19427] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19428] Chan, S. Y.; Empig, C. J.; Welte, F. J.; Speck, R. F.; Schmaljohn, A.; Kreisberg, J. F.; Goldsmith, M. A. : Folate receptor- $\alpha$  is a cofactor for cellular entry by Marburg and Ebola viruses. *Cell* 106: 117–126, 2001. ; and

[19429] Piedrahita, J. A.; Oetama, B.; Bennett, G. D.; van Waes, J.; Kamen, B. A.; Richardson, J.; Lacey, S. W.; Anderson, R. G. W.; Finnell, R. H. : Mice lacking the folic acid-binding protein.

[19430] Further studies establishing the function and utilities of FOLR1 are found in John Hopkins OMIM database record ID 136430, and in cited publications numbered 11715–11717, 11877–11881, 3591, 359 and 11714–3595 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Phosphatase 2 (formerly 2A), Catalytic Subunit, Alpha Isoform (PPP2CA, Accession NM\_002715) is

another VGAM399 host target gene. PPP2CA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2CA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2CA BINDING SITE, designated SEQ ID:8581, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19431] Another function of VGAM399 is therefore inhibition of Protein Phosphatase 2 (formerly 2A), Catalytic Subunit, Alpha Isoform (PPP2CA, Accession NM\_002715), a gene which plays a role in the regulation of most major metabolic pathways. Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2CA. The function of PPP2CA has been established by previous studies. Protein phosphorylation, a crucial posttranslational modification step controlling many diverse cellular functions, is dependent on the opposing actions of protein kinases and protein phosphatases. The enzyme protein phosphatase 2A is 1 of 4 major protein phosphatases identified in the cytosol of eukaryotic cells which are responsible for the



dephosphorylation of serine and threonine residues in proteins. Although all 4 protein phosphatases, PP1, PP2A, PP2B, and PP2C, have overlapping substrate specificities in vitro, they can be distinguished by the use of inhibitor proteins and by their dependence on metal ions. PP1 is inhibited by nanomolar concentrations of 2 thermostable proteins, inhibitor 1 and inhibitor 2, whereas the type 2 phosphatases are unaffected by these inhibitors. The type 2 phosphatases can be distinguished by how their activity is regulated: PP2A activity is independent of metal ions, PP2B is activated by  $\text{Ca}^{2+}$ /calmodulin, and PP2C is activated by  $\text{Mg}^{2+}$  (Cohen and Cohen, 1989). Protein phosphatase 2A appears to play a role in the regulation of most major metabolic pathways, as well as translation, transcription, and control of transition from G2 to the M phase of the cell cycle. PP2A may function as either a tumor promoter or tumor suppressor, depending on the cell type or the transforming agent. The mammalian enzyme can be isolated as a catalytic subunit of 36 kD complexed to 1 regulatory subunit of 65 kD and to another regulatory subunit of varying molecular mass, depending on the tissue and the separation technique used. Two isoforms of the catalytic subunit of PP2A, alpha and beta (OMIM Ref.

No. 176916), are demonstrable in many mammalian species. The structures of these catalytic subunits show the highest evolutionary conservation of all known enzymes, supporting the idea that they may serve crucial functions. Stone et al. (1988) isolated the human cDNA for the PPP2CA subunit from lung and lung fibroblast libraries. The cDNA encodes a 309-amino acid polypeptide. Groves et al. (1999) reported that the crystal structure of the PPP2CA subunit at 2.3-angstrom resolution revealed the conformation of its 15 tandemly repeated 'heat' sequences, degenerate motifs of 39 amino acids present in a variety of proteins, including huntingtin (OMIM Ref. No. 143100) and importin-beta (see OMIM Ref. No. 602738). Individual motifs are composed of a pair of antiparallel alpha-helices that assemble in a mainly linear, repetitive fashion to form an elongated molecule characterized by a double layer of alpha-helices. The protein interaction interface is formed from the intrarepeat turns that are aligned to form a continuous ridge.

[19432] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19433] Cohen, P.; Cohen, P. T. W. : Protein phosphatases come of

age. J. Biol. Chem. 264: 21435–21438, 1989. ; and

[19434] Groves, M. R.; Hanlon, N.; Turowski, P.; Hemmings, B. A.; Barford, D. : The structure of the protein phosphatase 2A PR65/A subunit reveals the conformation of its 15 tandemly repeated HE.

[19435] Further studies establishing the function and utilities of PPP2CA are found in John Hopkins OMIM database record ID 176915, and in cited publications numbered 2522–2525 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. TAR (HIV) RNA Binding Protein 2 (TARBP2, Accession NM\_134324) is another VGAM399 host target gene. TARBP2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TARBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TARBP2 BINDING SITE, designated SEQ ID:28626, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19436] Another function of VGAM399 is therefore inhibition of TAR (HIV) RNA Binding Protein 2 (TARBP2, Accession NM\_134324), a gene which is involved in the regulation of

HIV replication. Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TARBP2. The function of TARBP2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM95.FLJ20136 (Accession NM\_017684) is another VGAM399 host target gene. FLJ20136 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20136, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20136 BINDING SITE, designated SEQ ID:19233, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19437] Another function of VGAM399 is therefore inhibition of FLJ20136 (Accession NM\_017684). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20136. KIAA0433 (Accession NM\_015216) is another VGAM399 host target gene. KIAA0433 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by KIAA0433, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0433 BINDING SITE, designated SEQ ID:17545, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19438] Another function of VGAM399 is therefore inhibition of KIAA0433 (Accession NM\_015216). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0433. KIAA0446 (Accession XM\_044155) is another VGAM399 host target gene. KIAA0446 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0446 BINDING SITE, designated SEQ ID:34143, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19439] Another function of VGAM399 is therefore inhibition of KIAA0446 (Accession XM\_044155). Accordingly, utilities

of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0446. KIAA1826 (Accession XM\_040784) is another VGAM399 host target gene. KIAA1826 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1826 BINDING SITE, designated SEQ ID:33375, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19440] Another function of VGAM399 is therefore inhibition of KIAA1826 (Accession XM\_040784). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1826. Kinesin Family Member 13B (KIF13B, Accession XM\_096266) is another VGAM399 host target gene. KIF13B BINDING SITE1 and KIF13B BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KIF13B, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the comple-

mentarity of the nucleotide sequences of KIF13B BINDING SITE1 and KIF13B BINDING SITE2, designated SEQ ID:40309 and SEQ ID:17581 respectively, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19441] Another function of VGAM399 is therefore inhibition of Kinesin Family Member 13B (KIF13B, Accession XM\_096266). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIF13B. LOC253675 (Accession XM\_172990) is another VGAM399 host target gene. LOC253675 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253675, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253675 BINDING SITE, designated SEQ ID:46262, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19442] Another function of VGAM399 is therefore inhibition of LOC253675 (Accession XM\_172990). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC253675. LOC255919 (Accession XM\_170794) is another VGAM399 host target gene. LOC255919 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255919, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255919 BINDING SITE, designated SEQ ID:45557, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19443] Another function of VGAM399 is therefore inhibition of LOC255919 (Accession XM\_170794). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255919. LOC91012 (Accession XM\_035503) is another VGAM399 host target gene. LOC91012 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91012, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91012 BINDING SITE, designated SEQ ID:32279, to the



nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19444] Another function of VGAM399 is therefore inhibition of LOC91012 (Accession XM\_035503). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91012. LOC92539 (Accession XM\_045632) is another VGAM399 host target gene. LOC92539 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92539, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92539 BINDING SITE, designated SEQ ID:34496, to the nucleotide sequence of VGAM399 RNA, herein designated VGAM RNA, also designated SEQ ID:3110.

[19445] Another function of VGAM399 is therefore inhibition of LOC92539 (Accession XM\_045632). Accordingly, utilities of VGAM399 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92539. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 400 (VGAM400) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19446] VGAM400 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM400 was detected is described hereinabove with reference to Figs. 1–8.

[19447] VGAM400 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM400 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19448] VGAM400 gene encodes a VGAM400 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM400 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM400 precursor RNA is designated SEQ ID:386, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:386 is located at position 4214 relative to the genome of Cryphonectria Hypovirus 1.

[19449] VGAM400 precursor RNA folds onto itself, forming VGAM400 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19450] An enzyme complex designated DICER COMPLEX, `dices` the VGAM400 folded precursor RNA into VGAM400 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM400 RNA is designated SEQ ID:3111, and is provided hereinbelow with reference to the sequence listing part.

[19451] VGAM400 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM400 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM400 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19452] VGAM400 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM400 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM400 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM400 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM400 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19453] The complementary binding of VGAM400 RNA, herein designated VGAM RNA, to host target binding sites on VGAM400 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM400 host target RNA into VGAM400 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19454] It is appreciated that VGAM400 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM400 host target genes. The mRNA of each one of this plurality of VGAM400 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM400 RNA, herein designated VGAM RNA, and which when bound by VGAM400 RNA causes inhibition of translation of respective one or more VGAM400 host target proteins.

[19455] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM400 gene, herein designated VGAM GENE, on one or more VGAM400 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19456] It is yet further appreciated that a function of VGAM400 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM400 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM400 correlate with, and may be deduced from, the identity of

the host target genes which VGAM400 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19457] Nucleotide sequences of the VGAM400 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM400 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM400 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM400 are further described hereinbelow with reference to Table 1.

[19458] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM400 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM400 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19459] As mentioned hereinabove with reference to Fig. 1, a function of VGAM400 gene, herein designated VGAM is inhibition of expression of VGAM400 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM400 correlate with, and may be deduced from, the identity of the target genes which VGAM400

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19460] Collagen, Type IV, Alpha 6 (COL4A6, Accession NM\_001847) is a VGAM400 host target gene. COL4A6 BINDING SITE1 and COL4A6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by COL4A6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COL4A6 BINDING SITE1 and COL4A6 BINDING SITE2, designated SEQ ID:7581 and SEQ ID:27357 respectively, to the nucleotide sequence of VGAM400 RNA, herein designated VGAM RNA, also designated SEQ ID:3111.

[19461] A function of VGAM400 is therefore inhibition of Collagen, Type IV, Alpha 6 (COL4A6, Accession NM\_001847). Accordingly, utilities of VGAM400 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COL4A6. LOC154084 (Accession XM\_098468) is another VGAM400 host target gene. LOC154084 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154084, corresponding to a HOST TARGET binding



site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154084 BINDING SITE, designated SEQ ID:41684, to the nucleotide sequence of VGAM400 RNA, herein designated VGAM RNA, also designated SEQ ID:3111.

[19462] Another function of VGAM400 is therefore inhibition of LOC154084 (Accession XM\_098468). Accordingly, utilities of VGAM400 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154084. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 401 (VGAM401) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19463] VGAM401 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM401 was detected is described hereinabove with reference to Figs. 1–8.

[19464] VGAM401 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus

1. VGAM401 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19465] VGAM401 gene encodes a VGAM401 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM401 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM401 precursor RNA is designated SEQ ID:387, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:387 is located at position 11685 relative to the genome of Cryphonectria Hypovirus 1.

[19466] VGAM401 precursor RNA folds onto itself, forming VGAM401 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19467] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM401 folded precursor RNA into VGAM401 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM401 RNA is designated SEQ ID:3112, and is provided hereinbelow with reference to the sequence listing part.

[19468] VGAM401 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM401 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM401 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19469] VGAM401 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM401 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM401 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM401 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM401 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[19470] The complementary binding of VGAM401 RNA, herein designated VGAM RNA, to host target binding sites on VGAM401 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM401 host target RNA into VGAM401 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19471] It is appreciated that VGAM401 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM401 host target genes. The mRNA of each one of this plurality of VGAM401 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM401 RNA, herein designated VGAM RNA, and which when bound by VGAM401 RNA causes inhibition of translation of respective one or more VGAM401 host target proteins.

[19472] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM401 gene, herein designated VGAM GENE, on one or more VGAM401 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19473] It is yet further appreciated that a function of VGAM401 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM401 correlate with, and may be deduced from, the identity of the host target genes which VGAM401 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19474] Nucleotide sequences of the VGAM401 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM401 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM401 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM401 are further described hereinbelow with reference to Table 1.

- [19475] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM401 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM401 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19476] As mentioned hereinabove with reference to Fig. 1, a function of VGAM401 gene, herein designated VGAM is inhibition of expression of VGAM401 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM401 correlate with, and may be deduced from, the identity of the target genes which VGAM401 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [19477] V-akt Murine Thymoma Viral Oncogene Homolog 1 (AKT1, Accession NM\_005163) is a VGAM401 host target gene. AKT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKT1 BINDING SITE, designated SEQ ID:11654,

to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19478] A function of VGAM401 is therefore inhibition of V-akt Murine Thymoma Viral Oncogene Homolog 1 (AKT1, Accession NM\_005163), a gene which Serine-threonine protein kinase. Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKT1. The function of AKT1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM188.ATPase, Cu++ Transporting, Alpha Polypeptide (Menkes syndrome) (ATP7A, Accession NM\_000052) is another VGAM401 host target gene. ATP7A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP7A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP7A BINDING SITE, designated SEQ ID:5501, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19479] Another function of VGAM401 is therefore inhibition of



ATPase, Cu++ Transporting, Alpha Polypeptide (Menkes syndrome) (ATP7A, Accession NM\_000052). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP7A. Cas-Br-M (murine) Ecotropic Retroviral Transforming Sequence B (CBLB, Accession NM\_004351) is another VGAM401 host target gene. CBLB BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CBLB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CBLB BINDING SITE, designated SEQ ID:10553, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19480] Another function of VGAM401 is therefore inhibition of Cas-Br-M (murine) Ecotropic Retroviral Transforming Sequence B (CBLB, Accession NM\_004351), a gene which SH3 binding protein with similarity to human CBL; interacts and regulates signal transduction proteins. Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBLB. The function of CBLB has been established

by previous studies. The autoimmune disease type 1 diabetes mellitus, also known as insulin-dependent diabetes mellitus (IDDM; 222100), has a multifactorial etiology. The major histocompatibility complex (MHC) has been identified as a major susceptibility locus in the disease and its animal models. The Komeda diabetes-prone (KDP) rat is a spontaneous animal model of human type 1 diabetes (Komeda et al., 1998) in which the major susceptibility locus Iddm/kdp1 accounts, in combination with MHC, for most of the genetic predisposition to diabetes. Yokoi et al. (2002) reported positional cloning of Iddm/kdp1 and identification of a nonsense mutation in Cblb. Lymphocytes of the KDP rat infiltrate pancreatic islets and several tissues including thyroid gland and kidney, indicating autoimmunity. Similar findings in Cblb-deficient mice are caused by enhanced T-cell activation. Transgenic complementation with wildtype Cblb significantly suppressed development of the KDP phenotype. Thus, Cblb functions as a negative regulator of autoimmunity and Cblb is a major susceptibility gene for type 1 diabetes in the rat. Yokoi et al. (2002) concluded that impairment of the Cblb signaling pathway may contribute to human autoimmune diseases, including type 1 diabetes. Animal model experi-

ments lend further support to the function of CBLB. Bachmaier et al. (2000) generated mice deficient in CBLB by targeted disruption. At 6 months of age, these mice, which were maintained under specific pathogen-free conditions, exhibited a huge mass in submandibular salivary glands which resulted from accumulations of T and B cells and lymphoid neoorganogenesis. Mononuclear cells also accumulated in and damaged multiple organs and tissues, although the enlargement was only slight in spleen and lymph nodes. In CBLB +/- mice, the authors detected minor infiltration in only the submandibular salivary glands and kidneys. Measurement of a number of in vitro parameters demonstrated hyperproliferation of T and B cells as well as hyperproduction of IL2 but not of IFNG (OMIM Ref. No. 147570) or TNFA (OMIM Ref. No. 191160).

[19481] It is appreciated that the abovementioned animal model for CBLB is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[19482] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19483] Yokoi, N.; Komeda, K.; Wang, H.-Y.; Yano, H.; Kitada, K.;

Saitoh, Y.; Seino, Y.; Yasuda, K.; Serikawa, T.; Seino, S. :  
Cblb is a major susceptibility gene for rat type 1 diabetes  
mellitus. Nature Genet. 31: 391–394, 2002. ; and

[19484] Bachmaier, K.; Krawczyk, C.; Kozieradzki, I.; Kong, Y.-Y.;  
Sasaki, T.; Oliveira-dos-Santos, A.; Mariathasan, S.;  
Bouchard, D.; Wakeham, A.; Itie, A.; Le, J.; Ohashi, P. S.;  
Sarosi, I.;

[19485] Further studies establishing the function and utilities of  
CBLB are found in John Hopkins OMIM database record ID  
604491, and in cited publications numbered 4751–4755  
listed in the bibliography section hereinbelow, which are  
also hereby incorporated by reference. Optic Atrophy 1  
(autosomal dominant) (OPA1, Accession NM\_130833) is  
another VGAM401 host target gene. OPA1 BINDING SITE1  
through OPA1 BINDING SITE5 are HOST TARGET binding  
sites found in untranslated regions of mRNA encoded by  
OPA1, corresponding to HOST TARGET binding sites such  
as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-  
ble 2 illustrates the complementarity of the nucleotide se-  
quences of OPA1 BINDING SITE1 through OPA1 BINDING  
SITE5, designated SEQ ID:28325, SEQ ID:28333, SEQ  
ID:28341, SEQ ID:28349 and SEQ ID:28357 respectively,  
to the nucleotide sequence of VGAM401 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3112.

[19486] Another function of VGAM401 is therefore inhibition of Optic Atrophy 1 (autosomal dominant) (OPA1, Accession NM\_130833). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OPA1. DKFZP434P1750 (Accession NM\_015527) is another VGAM401 host target gene. DKFZP434P1750 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434P1750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434P1750 BINDING SITE, designated SEQ ID:17794, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19487] Another function of VGAM401 is therefore inhibition of DKFZP434P1750 (Accession NM\_015527). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434P1750. HCA3 (Accession NM\_138703) is another VGAM401 host target gene. HCA3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated

region of mRNA encoded by HCA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCA3 BINDING SITE, designated SEQ ID:28951, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19488] Another function of VGAM401 is therefore inhibition of HCA3 (Accession NM\_138703). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCA3. KIAA0876 (Accession XM\_035625) is another VGAM401 host target gene. KIAA0876 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0876, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0876 BINDING SITE, designated SEQ ID:32300, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19489] Another function of VGAM401 is therefore inhibition of KIAA0876 (Accession XM\_035625). Accordingly, utilities

of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0876. MGC12981 (Accession NM\_032357) is another VGAM401 host target gene. MGC12981 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC12981, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC12981 BINDING SITE, designated SEQ ID:26143, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19490] Another function of VGAM401 is therefore inhibition of MGC12981 (Accession NM\_032357). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC12981. NAG14 (Accession NM\_022143) is another VGAM401 host target gene. NAG14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NAG14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAG14 BINDING SITE,

designated SEQ ID:22706, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19491] Another function of VGAM401 is therefore inhibition of NAG14 (Accession NM\_022143). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAG14. Suppression of Tumorigenicity 7 Like (ST7L, Accession NM\_138727) is another VGAM401 host target gene. ST7L BINDING SITE1 through ST7L BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ST7L, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ST7L BINDING SITE1 through ST7L BINDING SITE3, designated SEQ ID:28979, SEQ ID:29210 and SEQ ID:19337 respectively, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19492] Another function of VGAM401 is therefore inhibition of Suppression of Tumorigenicity 7 Like (ST7L, Accession NM\_138727). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clini-



cal conditions associated with ST7L. LOC90593 (Accession XM\_032815) is another VGAM401 host target gene.

LOC90593 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90593, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90593 BINDING SITE, designated SEQ ID:31766, to the nucleotide sequence of VGAM401 RNA, herein designated VGAM RNA, also designated SEQ ID:3112.

[19493] Another function of VGAM401 is therefore inhibition of LOC90593 (Accession XM\_032815). Accordingly, utilities of VGAM401 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90593. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 402 (VGAM402) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19494] VGAM402 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM402 was detected is described hereinabove with reference to Figs. 1–8.

[19495] VGAM402 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM402 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19496] VGAM402 gene encodes a VGAM402 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM402 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM402 precursor RNA is designated SEQ ID:388, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:388 is located at position 6807 relative to the genome of Cryphonectria Hypovirus 1.

[19497] VGAM402 precursor RNA folds onto itself, forming VGAM402 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19498] An enzyme complex designated DICER COMPLEX, `dices` the VGAM402 folded precursor RNA into VGAM402 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM402 RNA is designated SEQ ID:3113, and is provided hereinbelow with reference to the sequence listing part.

[19499] VGAM402 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM402 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM402 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19500] VGAM402 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM402 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM402 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM402 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM402 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19501] The complementary binding of VGAM402 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM402 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM402 host target RNA into VGAM402 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19502] It is appreciated that VGAM402 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM402 host target genes. The mRNA of each one of this plurality of VGAM402 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM402 RNA, herein designated VGAM RNA, and which when bound by VGAM402 RNA causes inhibition of translation of respective one or more VGAM402 host target proteins.

[19503] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM402 gene, herein designated VGAM GENE, on one or more VGAM402 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19504] It is yet further appreciated that a function of VGAM402 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM402 correlate with, and may be deduced from, the identity of the host target genes which VGAM402 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19505] Nucleotide sequences of the VGAM402 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM402 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM402 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM402 are further described hereinbelow with reference to Table 1.

[19506] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM402 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM402 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19507] As mentioned hereinabove with reference to Fig. 1, a function of VGAM402 gene, herein designated VGAM is inhibition of expression of VGAM402 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM402 correlate with, and may be deduced from, the identity of the target genes which VGAM402 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19508] HUS1 Checkpoint Homolog (*S. pombe*) (HUS1, Accession XM\_165873) is a VGAM402 host target gene. HUS1 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by HUS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HUS1 BINDING SITE, designated SEQ ID:43790, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19509] A function of VGAM402 is therefore inhibition of HUS1 Checkpoint Homolog (*S. pombe*) (HUS1, Accession XM\_165873), a gene which May form DNA damage-responsive protein complex . Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUS1. The function of HUS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM228.N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243) is another VGAM402 host target gene. NDRG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NDRG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide



sequences of NDRG1 BINDING SITE, designated SEQ ID:29970, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19510] Another function of VGAM402 is therefore inhibition of N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243), a gene which may have a growth inhibitory role. Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDRG1. The function of NDRG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM144.HSPC138 (Accession NM\_016401) is another VGAM402 host target gene. HSPC138 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HSPC138, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC138 BINDING SITE, designated SEQ ID:18538, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19511] Another function of VGAM402 is therefore inhibition of HSPC138 (Accession NM\_016401). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC138. HSPC251 (Accession NM\_016505) is another VGAM402 host target gene. HSPC251 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HSPC251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC251 BINDING SITE, designated SEQ ID:18584, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19512] Another function of VGAM402 is therefore inhibition of HSPC251 (Accession NM\_016505). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC251. IDN3 (Accession NM\_133433) is another VGAM402 host target gene. IDN3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by IDN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of IDN3 BINDING SITE, designated SEQ ID:28512, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19513] Another function of VGAM402 is therefore inhibition of IDN3 (Accession NM\_133433). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IDN3. KIAA0284 (Accession XM\_032235) is another VGAM402 host target gene. KIAA0284 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0284, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0284 BINDING SITE, designated SEQ ID:31620, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19514] Another function of VGAM402 is therefore inhibition of KIAA0284 (Accession XM\_032235). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0284. KIAA0844 (Accession NM\_014951) is another VGAM402 host target gene. KIAA0844 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0844, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0844 BINDING SITE, designated SEQ ID:17285, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19515] Another function of VGAM402 is therefore inhibition of KIAA0844 (Accession NM\_014951). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0844. KIAA1068 (Accession NM\_015332) is another VGAM402 host target gene. KIAA1068 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1068, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1068 BINDING SITE, designated SEQ ID:17645, to the nucleotide sequence of VGAM402 RNA, herein designated

VGAM RNA, also designated SEQ ID:3113.

[19516] Another function of VGAM402 is therefore inhibition of KIAA1068 (Accession NM\_015332). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1068. KIAA1169 (Accession NM\_017901) is another VGAM402 host target gene. KIAA1169 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1169, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1169 BINDING SITE, designated SEQ ID:19566, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19517] Another function of VGAM402 is therefore inhibition of KIAA1169 (Accession NM\_017901). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1169. KIAA1305 (Accession NM\_025081) is another VGAM402 host target gene. KIAA1305 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1305, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1305 BINDING SITE, designated SEQ ID:24682, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19518] Another function of VGAM402 is therefore inhibition of KIAA1305 (Accession NM\_025081). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1305. KIAA1881 (Accession XM\_170901) is another VGAM402 host target gene. KIAA1881 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1881, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1881 BINDING SITE, designated SEQ ID:45656, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19519] Another function of VGAM402 is therefore inhibition of KIAA1881 (Accession XM\_170901). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1881. KIAA1932 (Accession XM\_055900) is another VGAM402 host target gene. KIAA1932 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1932, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1932 BINDING SITE, designated SEQ ID:36351, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19520] Another function of VGAM402 is therefore inhibition of KIAA1932 (Accession XM\_055900). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1932. PB1 (Accession NM\_018165) is another VGAM402 host target gene. PB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PB1 BINDING SITE, designated SEQ ID:19983, to the nucleotide sequence of

VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19521] Another function of VGAM402 is therefore inhibition of PB1 (Accession NM\_018165). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PB1. Zinc Finger, DHHC Domain Containing 8 (ZDHHC8, Accession XM\_033828) is another VGAM402 host target gene. ZDHHC8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZDHHC8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZDHHC8 BINDING SITE, designated SEQ ID:31963, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19522] Another function of VGAM402 is therefore inhibition of Zinc Finger, DHHC Domain Containing 8 (ZDHHC8, Accession XM\_033828). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZDHHC8. LOC145547 (Accession XM\_085167) is another VGAM402 host target



gene. LOC145547 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145547, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145547 BINDING SITE, designated SEQ ID:37892, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19523] Another function of VGAM402 is therefore inhibition of LOC145547 (Accession XM\_085167). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145547. LOC152765 (Accession XM\_087519) is another VGAM402 host target gene. LOC152765 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152765, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152765 BINDING SITE, designated SEQ ID:39314, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19524] Another function of VGAM402 is therefore inhibition of LOC152765 (Accession XM\_087519). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152765. LOC161635 (Accession XM\_172921) is another VGAM402 host target gene. LOC161635 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC161635, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161635 BINDING SITE, designated SEQ ID:46185, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19525] Another function of VGAM402 is therefore inhibition of LOC161635 (Accession XM\_172921). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161635. LOC253842 (Accession XM\_173230) is another VGAM402 host target gene. LOC253842 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253842, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253842 BINDING SITE, designated SEQ ID:46504, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19526] Another function of VGAM402 is therefore inhibition of LOC253842 (Accession XM\_173230). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253842. LOC91149 (Accession XM\_036480) is another VGAM402 host target gene. LOC91149 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91149, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91149 BINDING SITE, designated SEQ ID:32452, to the nucleotide sequence of VGAM402 RNA, herein designated VGAM RNA, also designated SEQ ID:3113.

[19527] Another function of VGAM402 is therefore inhibition of LOC91149 (Accession XM\_036480). Accordingly, utilities of VGAM402 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC91149. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 403 (VGAM403) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19528] VGAM403 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM403 was detected is described hereinabove with reference to Figs. 1–8.

[19529] VGAM403 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM403 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19530] VGAM403 gene encodes a VGAM403 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM403 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM403 precursor RNA is designated SEQ ID:389, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:389 is located at position 9304 relative to the genome of Cryphonectria Hypovirus 1.

[19531] VGAM403 precursor RNA folds onto itself, forming VGAM403 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19532] An enzyme complex designated DICER COMPLEX, `dices` the VGAM403 folded precursor RNA into VGAM403 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 59%) nucleotide sequence of VGAM403 RNA is designated SEQ ID:3114, and is provided hereinbelow with reference to the sequence listing part.

[19533] VGAM403 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM403 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM403 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19534] VGAM403 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM403 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM403 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM403 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM403 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[19535] The complementary binding of VGAM403 RNA, herein designated VGAM RNA, to host target binding sites on VGAM403 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM403 host target RNA into VGAM403 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19536] It is appreciated that VGAM403 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM403 host target genes. The mRNA of each one of this plurality of VGAM403 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM403 RNA, herein designated VGAM RNA, and which when bound by VGAM403 RNA causes in-

hibition of translation of respective one or more VGAM403 host target proteins.

[19537] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM403 gene, herein designated VGAM GENE, on one or more VGAM403 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19538] It is yet further appreciated that a function of VGAM403 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM403 include diagnosis, prevention and



treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM403 correlate with, and may be deduced from, the identity of the host target genes which VGAM403 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19539] Nucleotide sequences of the VGAM403 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM403 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM403 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM403 are further described hereinbelow with reference to Table 1.

[19540] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM403 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM403 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19541] As mentioned hereinabove with reference to Fig. 1, a function of VGAM403 gene, herein designated VGAM is inhibition of expression of VGAM403 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM403 correlate with, and may be deduced from, the identity of the target genes which VGAM403 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19542] Cyclin-dependent Kinase 5, Regulatory Subunit 2 (p39) (CDK5R2, Accession NM\_003936) is a VGAM403 host target gene. CDK5R2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDK5R2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDK5R2 BINDING SITE, designated SEQ ID:10044, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19543] A function of VGAM403 is therefore inhibition of Cyclin-dependent Kinase 5, Regulatory Subunit 2 (p39) (CDK5R2, Accession NM\_003936), a gene which acts as a regulatory subunit for the cyclin-dependent CDK5. Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDK5R2. The function of CDK5R2 has been established by

previous studies. Neuronal CDC2 (OMIM Ref. No. 116940)–like kinase is a heterodimer of CDK5 (OMIM Ref. No. 123831) and p25(nck5a), a neuron–specific 25–kD regulatory subunit derived proteolytically from NCK5A (neuronal CDK5 activator; 603460). By screening a human hippocampus library with a bovine Nck5a cDNA, Tang et al. (1995) isolated cDNAs encoding NCK5AI, a distinct NCK5A isoform. They also referred to the protein as p39(OMIM Ref. No. nck5ai) based on its calculated molecular mass of 39 kD. The predicted 367–amino acid p39(OMIM Ref. No. nck5ai) protein shares 57% sequence identity with human NCK5A. As does p25(nck5a), a 30–kD truncated form of p39(OMIM Ref. No. nck5ai) activated both recombinant and native CDK5 in vitro. Northern blot analysis of rat tissues indicated that both Nck5A and p39(OMIM Ref. No. nck5ai) are expressed exclusively in brain. In situ hybridization to rat brain sections revealed that p39(OMIM Ref. No. nck5ai) mRNA was highly expressed in the CA1 to CA3 zone of hippocampal formation, an area highly enriched in neurons. There was no expression in the fimbria hippocampi, where glial cells predominate. Tang et al. (1995) concluded that p39(OMIM Ref. No. nck5ai) shares many common characteristics with

NCK5A, including CDK5-activating activity and brain- and neuron-specific expression. Nilden et al. (1998) identified Cdk5r2, the mouse gene homologous to human p39(OMIM Ref. No. nck5ai). The coding region of Cdk5r2 is contained within a single exon. The predicted mouse and human proteins are 95% identical.

[19544] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19545] Muravenko, O. V.; Gizatullin, R. Z.; Protopopov, A. I.; Kashuba, V. I.; Zabarovsky, E. R.; Zelenin, A. V. : Assignment of CDK5R2 coding for the cyclin-dependent kinase 5, regulatory subunit 2 (NCK5AI protein) to human chromosome band 2q35 by fluorescent in situ hybridization. Cytogenet. Cell Genet. 89: 160-161, 2000. ; and

[19546] Tang, D.; Yeung, J.; Lee, K-Y.; Matsushita, M.; Matsui, H.; Tomizawa, K.; Hatase, O.; Wang, J. H. : An isoform of the neuronal cyclin-dependent kinase 5 (Cdk5) activator. J. Biol. Chem.

[19547] Further studies establishing the function and utilities of CDK5R2 are found in John Hopkins OMIM database record ID 603764, and in cited publications numbered 7950-7952 listed in the bibliography section hereinbelow,

which are also hereby incorporated by reference. Winged-helix Nude (WHN, Accession NM\_003593) is another VGAM403 host target gene. WHN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WHN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WHN BINDING SITE, designated SEQ ID:9651, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19548] Another function of VGAM403 is therefore inhibition of Winged-helix Nude (WHN, Accession NM\_003593), a gene which plays a role in transcriptional regulation. Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WHN. The function of WHN has been established by previous studies. In 2 sisters with T-cell immunodeficiency, congenital alopecia, and nail dystrophy (OMIM Ref. No. 601705), Frank et al. (1999) identified a homozygous nonsense mutation in the WHN gene. In mammals, whn expression occurs in epithelial cells of the thymus as well as specific cells of the hair follicle. In the human, WHN is

expressed in the differentiating cells of the hair follicle precortex and the innermost cell layer of the outer root sheath. Expression in the thymus was not determined. Animal model experiments lend further support to the function of WHN. Mutations at the 'nude' locus of mice and rats disrupt normal hair growth and thymus development, causing nude mice and rats to be immune-deficient.

Nehls et al. (1994) showed that a gene designated whn, located in the region of mouse chromosome 11 known to contain the nude locus, encodes a new member of the winged-helix domain family of transcription factors. The predicted protein is 648 amino acids long. The whn gene was disrupted on the mouse and rat nude alleles. Mutant transcripts did not encode the characteristic DNA-binding domain, strongly suggesting that the whn gene is the nude gene. Mutations in winged-helix domain genes cause homeotic transformations in *Drosophila* and distort cell-fate decisions during vulval development in *C. elegans*. The whn gene was thus the first member of this class of genes to be implicated in a specific developmental defect in vertebrates

[19549] It is appreciated that the abovementioned animal model for WHN is acknowledged by those skilled in the art as a

scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[19550] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19551] Frank, J.; Pignata, C.; Panteleyev, A. A.; Prowse, D. M.; Baden, H.; Weiner, L.; Gaetaniello, L.; Ahmad, W.; Pozzi, N.; Caerhalmi-Friedman, P. B.; Aita, V. M.; Uyttendaele, H.; Gordon, D.; Ott, J.; Brisette, J. L.; Christiano, A. M. : Exposing the human nude phenotype. Nature 398: 473-474, 1999. ; and

[19552] Nehls, M.; Pfeifer, D.; Schorpp, M.; Hedrich, H.; Boehm, T. : New member of the winged-helix protein family disrupted in mouse and rat nude mutations. Nature 372: 103-107, 1994.

[19553] Further studies establishing the function and utilities of WHN are found in John Hopkins OMIM database record ID 600838, and in cited publications numbered 9595-9600 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Apolipoprotein L, 4 (APOL4, Accession NM\_030643) is another VGAM403 host target gene. APOL4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by APOL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APOL4 BINDING SITE, designated SEQ ID:24980, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19554] Another function of VGAM403 is therefore inhibition of Apolipoprotein L, 4 (APOL4, Accession NM\_030643). Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOL4. DCOHM (Accession NM\_032151) is another VGAM403 host target gene. DCOHM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DCOHM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DCOHM BINDING SITE, designated SEQ ID:25849, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19555] Another function of VGAM403 is therefore inhibition of DCOHM (Accession NM\_032151). Accordingly, utilities of



VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DCOHM. FLJ22028 (Accession NM\_024854) is another VGAM403 host target gene. FLJ22028 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22028 BINDING SITE, designated SEQ ID:24287, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19556] Another function of VGAM403 is therefore inhibition of FLJ22028 (Accession NM\_024854). Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22028. KIAA0441 (Accession NM\_014797) is another VGAM403 host target gene. KIAA0441 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0441, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0441 BINDING SITE,

designated SEQ ID:16716, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19557] Another function of VGAM403 is therefore inhibition of KIAA0441 (Accession NM\_014797). Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0441. Ring Finger Protein 34 (RNF34, Accession NM\_025126) is another VGAM403 host target gene. RNF34 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNF34, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF34 BINDING SITE, designated SEQ ID:24770, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19558] Another function of VGAM403 is therefore inhibition of Ring Finger Protein 34 (RNF34, Accession NM\_025126). Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNF34. Syntaxin 12 (STX12, Accession

XM\_039018) is another VGAM403 host target gene. STX12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STX12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STX12 BINDING SITE, designated SEQ ID:32984, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19559] Another function of VGAM403 is therefore inhibition of Syntaxin 12 (STX12, Accession XM\_039018). Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STX12. LOC146733 (Accession XM\_097076) is another VGAM403 host target gene. LOC146733 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146733, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146733 BINDING SITE, designated SEQ ID:40725, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19560] Another function of VGAM403 is therefore inhibition of LOC146733 (Accession XM\_097076). Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146733. LOC219686 (Accession XM\_165544) is another VGAM403 host target gene. LOC219686 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219686, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219686 BINDING SITE, designated SEQ ID:43678, to the nucleotide sequence of VGAM403 RNA, herein designated VGAM RNA, also designated SEQ ID:3114.

[19561] Another function of VGAM403 is therefore inhibition of LOC219686 (Accession XM\_165544). Accordingly, utilities of VGAM403 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219686. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 404 (VGAM404) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[19562] VGAM404 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM404 was detected is described hereinabove with reference to Figs. 1–8.

[19563] VGAM404 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM404 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19564] VGAM404 gene encodes a VGAM404 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM404 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM404 precursor RNA is designated SEQ ID:390, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:390 is located at position 7366 relative to the genome of Cryphonectria Hypovirus 1.

[19565] VGAM404 precursor RNA folds onto itself, forming VGAM404 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[19566] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM404 folded precursor RNA into VGAM404 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 43%) nucleotide se-  
quence of VGAM404 RNA is designated SEQ ID:3115, and  
is provided hereinbelow with reference to the sequence  
listing part.

[19567] VGAM404 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM404 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM404 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19568] VGAM404 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM404 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM404 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM404 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM404 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19569] The complementary binding of VGAM404 RNA, herein designated VGAM RNA, to host target binding sites on VGAM404 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM404 host target RNA into VGAM404 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19570] It is appreciated that VGAM404 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM404 host target genes. The mRNA of each one of this plurality of VGAM404 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM404 RNA, herein designated VGAM RNA, and which when bound by VGAM404 RNA causes inhibition of translation of respective one or more VGAM404 host target proteins.

[19571] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by



VGAM404 gene, herein designated VGAM GENE, on one or more VGAM404 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19572] It is yet further appreciated that a function of VGAM404 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM404 correlate with, and may be deduced from, the identity of the host target genes which VGAM404 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

- [19573] Nucleotide sequences of the VGAM404 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM404 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM404 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM404 are further described hereinbelow with reference to Table 1.
- [19574] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM404 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM404 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19575] As mentioned hereinabove with reference to Fig. 1, a function of VGAM404 gene, herein designated VGAM is inhibition of expression of VGAM404 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM404 correlate with, and may be deduced from, the identity of the target genes which VGAM404 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19576] F-box and Leucine-rich Repeat Protein 11 (FBXL11, Accession NM\_012308) is a VGAM404 host target gene. FBXL11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FBXL11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXL11 BINDING SITE, designated SEQ ID:14680, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19577] A function of VGAM404 is therefore inhibition of F-box and Leucine-rich Repeat Protein 11 (FBXL11, Accession NM\_012308), a gene which are BTB/POZ domain-containing zinc finger proteins implicated in oncogenesis. Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXL11. The function of FBXL11 has been established by previous studies. The F box, named after cyclin F (CCNF; 600227), in which it was originally observed, is an approximately 40-amino acid motif that binds SKP1 (OMIM Ref. No. 601434). F-box proteins are components of modular E3 ubiquitin protein ligases called

SCFs (SKP1, OMIM Ref. No. 603134), F-box proteins), which function in phosphorylation-dependent ubiquitination. Using a yeast 2-hybrid screen with SKP1 as bait, followed by searching sequence databases, Winston et al. (1999) and Cenciarelli et al. (1999) identified 33 mammalian and 26 human F-box proteins, respectively. These contained C termini with leucine-rich repeats (FBXLs, e.g., SKP2 (OMIM Ref. No. 601436)), WD40 domains (FBXWs, e.g., BTRCP (OMIM Ref. No. 603482)), or no recognizable motifs (FBXOs, e.g., CCNF). By searching sequence databases, Ilyin et al. (2000) identified a cDNA encoding FBXL11, which they referred to as FBL7. They predicted that FBXL11, which is identical to the 496-amino acid KIAA1004 protein reported by Nagase et al. (1999), contains at least 6 highly degenerated leucine-rich repeats. By RT-PCR analysis, Nagase et al. (1999) detected ubiquitous expression of FBXL11, with highest levels in brain, testis, and ovary, followed by lung; lowest expression was in pancreas. Within brain, expression was highest in cerebellum and subthalamic nuclei. The International Radiation Hybrid Mapping Consortium mapped the FBXL11 gene to chromosome 11 (sts-Z40471).

[19578] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

[19579] Ilyin, G. P.; Rialland, M.; Pigeon, C.; Guguen-Guillouzo, C. : cDNA cloning and expression analysis of new members of the mammalian F-box protein family. *Genomics* 67: 40-47, 2000. ; and

[19580] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Hiro-sawa, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human ge.

[19581] Further studies establishing the function and utilities of FBXL11 are found in John Hopkins OMIM database record ID 605657, and in cited publications numbered 409, 827 and 8593 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1 (GalNAc-T1) (GALNT1, Accession NM\_020474) is another VGAM404 host target gene. GALNT1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GALNT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of GALNT1 BINDING SITE, designated SEQ ID:21723, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19582] Another function of VGAM404 is therefore inhibition of UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1 (GalNAc-T1) (GALNT1, Accession NM\_020474), a gene which transfers an N-acetyl galactosamine (GalNAc) to a serine or threonine residue in the first step of O-linked oligosaccharide biosynthesis. Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GALNT1. The function of GALNT1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM120.Rab Geranylgeranyltransferase, Alpha Subunit (RABGGTA, Accession NM\_004581) is another VGAM404 host target gene. RABGGTA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RABGGTA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of RABGGTA BINDING SITE, designated SEQ ID:10930, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19583] Another function of VGAM404 is therefore inhibition of Rab Geranylgeranyltransferase, Alpha Subunit (RABGGTA, Accession NM\_004581), a gene which is the alpha subunit of geranylgeranyl transferase. Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RABGGTA. The function of RABGGTA has been established by previous studies. Van Bokhoven et al. (1996) cloned the human RABGGTA gene from a fetal brain library. The gene encodes a 567-amino acid polypeptide. Homology to the transglutaminase gene, TGM1 (OMIM Ref. No. 190195), which maps to 14q11, indicated that this subunit was located on the same chromosomal band; Southern blot analysis confirmed this locus. Van Bokhoven et al. (1996) found that the 3-prime end of the RABGGTA cDNA sequence overlaps the promoter region of TGM1. Further analysis revealed that the RABGGTA and TGM1 genes are located only 2 kb apart in head-to-tail tandem arrangement; however, these 2 genes are not likely to be func-

tionally related. Animal model experiments lend further support to the function of RABGGTA. Mice homozygous for 'gunmetal' (gm), a spontaneous, recessive mutation, have prolonged bleeding caused by defects in platelets and megakaryocytes (Swank et al., 1993; Novak et al., 1995). These mice also have macrothrombocytopenia and reduced platelet alpha- and delta-granule contents (storage pool deficiency, SPD). Megakaryocytes, the progenitors of platelets, are more plentiful in gm mice, but have abnormal intracellular membranes, increased emperipolesis (the active movement of 1 cell through another), and decreased platelet synthesis. In addition, gm homozygotes have partial cutaneous albinism, the feature that gives the mutation its name. Detter et al. (2000) noted that the phenotype resembles human gray platelet syndrome (GPS; 139090) and platelet alpha- and delta-SPD (OMIM Ref. No. 185050).

[19584] It is appreciated that the abovementioned animal model for RABGGTA is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[19585] Full details of the abovementioned studies are described in the following publications, the disclosure of which are



hereby incorporated by reference:

- [19586] Detter, J. C.; Zhang, Q.; Mules, E. H.; Novak, E. K.; Mishra, V. S.; Li, W.; McMurtrie, E. B.; Tchernev, V. T.; Wallace, M. R.; Seabra, M. C.; Swank, R. T.; Kingsmore, S. F. : Rab geranylgeranyl transferase alpha mutation in the gunmetal mouse reduces Rab prenylation and platelet synthesis. Proc. Nat. Acad. Sci. 97: 4144–4149, 2000. ; and
- [19587] van Bokhoven, H.; Rawson, R. B.; Merkx, G. F. M.; Cremers, F. P. M.; Seabra, M. C. : cDNA cloning and chromosomal localization of the genes encoding the alpha- and beta-subunits of huma.
- [19588] Further studies establishing the function and utilities of RABGGTA are found in John Hopkins OMIM database record ID 601905, and in cited publications numbered 8883–8884, 1187–118 and 8885 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Regulator of G-protein Signalling 3 (RGS3, Accession NM\_021106) is another VGAM404 host target gene. RGS3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RGS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of RGS3 BINDING SITE, designated SEQ ID:22087, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19589] Another function of VGAM404 is therefore inhibition of Regulator of G-protein Signalling 3 (RGS3, Accession NM\_021106), a gene which negatively regulates G protein-coupled receptor signalling. Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RGS3. The function of RGS3 has been established by previous studies. Chatterjee et al. (1997) stated that 17 mammalian RGS members had been identified by cloning or by comparison to expressed sequence tags (ESTs). They studied RGS3, the largest member of the RGS family to date. They found that the coding region of the human RGS3 gene spans 14.7 kb and contains 6 exons; the 5-prime untranslated region spans 3.2 kb and contains 2 exons. The RGS domain, conserved among all RGS proteins, is encoded by 3 exons, while the unique N-terminal domain of RGS3 is encoded by a single exon. Comparison of the locations of the intron-exon boundaries of the human RGS3 gene to those of the human RGS2 gene revealed a remarkable

similarity. Using 5-prime-RACE analysis, they mapped the transcription start site 517 bp upstream of the translation start site. Many potential regulatory elements were identified in the 5-prime flanking region. By screening a mouse embryonic cDNA library using the yeast 2-hybrid system with the cytoplasmic domain of ephrin-B2 (EFNB2; 600527) as bait, Lu et al. (2001) isolated cDNAs encoding a cytoplasmic protein they designated Pdз-Rgs3. Pdз-Rgs3 binds ephrin-B2 through a PDZ domain, and it has an RGS domain. The human homolog of Pdз-Rgs3, RGS3, had been described as a shorter sequence (Druey et al., 1996). Pdз-Rgs3 can mediate signaling from the ephrin-B cytoplasmic tail. The authors showed that SDF1 (OMIM Ref. No. 600835), a chemokine with a G protein-coupled receptor, and BDNF (OMIM Ref. No. 113505) are chemoattractants for cerebellar granule cells, and that SDF1 chemoattraction is selectively inhibited by soluble ephrin-B receptor (see OMIM Ref. No. 602757). This inhibition could be blocked by a truncated Pdз-Rgs3 protein lacking the RGS domain.

[19590] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [19591] Druey, K. M.; Blumer, K. J.; Kang, V. H.; Kehrl, J. H. : Inhibition of G-protein-mediated MAP kinase activation by a new mammalian gene family. *Nature* 379: 742–746, 1996.  
; and
- [19592] Chatterjee, T. K.; Eapen, A.; Kanis, A. B.; Fisher, R. A. : Genomic organization, 5-prime-flanking region, and chromosomal localization of the human RGS3 gene. *Genomics* 45: 429–433, 1997.
- [19593] Further studies establishing the function and utilities of RGS3 are found in John Hopkins OMIM database record ID 602189, and in cited publications numbered 5845–584 and 12564 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZP434H132 (Accession XM\_057020) is another VGAM404 host target gene. DKFZP434H132 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZP434H132, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434H132 BINDING SITE, designated SEQ ID:36446, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19594] Another function of VGAM404 is therefore inhibition of DKFZP434H132 (Accession XM\_057020). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434H132. KIAA1600 (Accession XM\_049351) is another VGAM404 host target gene. KIAA1600 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1600, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1600 BINDING SITE, designated SEQ ID:35392, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19595] Another function of VGAM404 is therefore inhibition of KIAA1600 (Accession XM\_049351). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1600. MGC2628 (Accession NM\_024076) is another VGAM404 host target gene. MGC2628 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC2628, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2628 BINDING SITE, designated SEQ ID:23508, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19596] Another function of VGAM404 is therefore inhibition of MGC2628 (Accession NM\_024076). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2628. Oxysterol Binding Protein-like 3 (OSBPL3, Accession NM\_015550) is another VGAM404 host target gene. OSBPL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OSBPL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSBPL3 BINDING SITE, designated SEQ ID:17815, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19597] Another function of VGAM404 is therefore inhibition of Oxysterol Binding Protein-like 3 (OSBPL3, Accession NM\_015550). Accordingly, utilities of VGAM404 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with OSBPL3. Synaptotagmin XII (SYT12, Accession XM\_170657) is another VGAM404 host target gene. SYT12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SYT12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYT12 BINDING SITE, designated SEQ ID:45431, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19598] Another function of VGAM404 is therefore inhibition of Synaptotagmin XII (SYT12, Accession XM\_170657). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYT12. LOC124976 (Accession XM\_058879) is another VGAM404 host target gene. LOC124976 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC124976, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC124976 BINDING SITE, designated SEQ ID:36782, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19599] Another function of VGAM404 is therefore inhibition of LOC124976 (Accession XM\_058879). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124976. LOC148114 (Accession XM\_086050) is another VGAM404 host target gene. LOC148114 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148114 BINDING SITE, designated SEQ ID:38465, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19600] Another function of VGAM404 is therefore inhibition of LOC148114 (Accession XM\_086050). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148114. LOC254428 (Accession XM\_170932) is another VGAM404 host target gene. LOC254428 BINDING



SITE is HOST TARGET binding site found in the 3` un-translated region of mRNA encoded by LOC254428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254428 BINDING SITE, designated SEQ ID:45715, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19601] Another function of VGAM404 is therefore inhibition of LOC254428 (Accession XM\_170932). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254428. LOC254945 (Accession XM\_173038) is another VGAM404 host target gene. LOC254945 BINDING SITE is HOST TARGET binding site found in the 5` un-translated region of mRNA encoded by LOC254945, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254945 BINDING SITE, designated SEQ ID:46304, to the nucleotide sequence of VGAM404 RNA, herein designated VGAM RNA, also designated SEQ ID:3115.

[19602] Another function of VGAM404 is therefore inhibition of

LOC254945 (Accession XM\_173038). Accordingly, utilities of VGAM404 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254945. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 405 (VGAM405) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19603] VGAM405 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM405 was detected is described hereinabove with reference to Figs. 1–8.

[19604] VGAM405 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM405 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19605] VGAM405 gene encodes a VGAM405 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM405 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM405 precursor RNA is designated SEQ ID:391, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:391 is located at position 3539 relative to the genome of Cryphonectria Hypovirus 1.

[19606] VGAM405 precursor RNA folds onto itself, forming VGAM405 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19607] An enzyme complex designated DICER COMPLEX, `dices` the VGAM405 folded precursor RNA into VGAM405 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide se-

quence of VGAM405 RNA is designated SEQ ID:3116, and is provided hereinbelow with reference to the sequence listing part.

[19608] VGAM405 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM405 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM405 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[19609] VGAM405 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM405 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM405 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM405 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM405 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[19610] The complementary binding of VGAM405 RNA, herein designated VGAM RNA, to host target binding sites on VGAM405 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM405 host target RNA into VGAM405 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19611] It is appreciated that VGAM405 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM405 host target genes. The mRNA of each one of this plurality of VGAM405 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM405 RNA, herein designated VGAM RNA, and which when bound by VGAM405 RNA causes inhibition of translation of respective one or more VGAM405 host target proteins.

[19612] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM405 gene, herein designated VGAM GENE, on one or more VGAM405 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19613] It is yet further appreciated that a function of VGAM405 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM405 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM405 correlate with, and may be deduced from, the identity of the host target genes which VGAM405 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19614] Nucleotide sequences of the VGAM405 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM405 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM405 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM405 are further described hereinbelow with reference to Table 1.

[19615] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM405 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM405 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19616] As mentioned hereinabove with reference to Fig. 1, a function of VGAM405 gene, herein designated VGAM is inhibition of expression of VGAM405 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM405 correlate with, and may be deduced from, the identity of the target genes which VGAM405 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19617] TOSO (Accession NM\_005449) is a VGAM405 host target gene. TOSO BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TOSO, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOSO BINDING SITE, designated SEQ ID:11935, to the nucleotide sequence of VGAM405 RNA, herein designated VGAM RNA, also designated SEQ ID:3116.

[19618] A function of VGAM405 is therefore inhibition of TOSO (Accession NM\_005449). Accordingly, utilities of VGAM405 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOSO. LOC152283 (Accession XM\_098196) is another VGAM405 host target gene. LOC152283 BINDING SITE is HOST TAR-



GET binding site found in the 5' untranslated region of mRNA encoded by LOC152283, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152283 BINDING SITE, designated SEQ ID:41484, to the nucleotide sequence of VGAM405 RNA, herein designated VGAM RNA, also designated SEQ ID:3116.

[19619] Another function of VGAM405 is therefore inhibition of LOC152283 (Accession XM\_098196). Accordingly, utilities of VGAM405 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152283. LOC255002 (Accession XM\_172994) is another VGAM405 host target gene. LOC255002 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255002, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255002 BINDING SITE, designated SEQ ID:46270, to the nucleotide sequence of VGAM405 RNA, herein designated VGAM RNA, also designated SEQ ID:3116.

[19620] Another function of VGAM405 is therefore inhibition of

LOC255002 (Accession XM\_172994). Accordingly, utilities of VGAM405 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255002. LOC92017 (Accession XM\_042234) is another VGAM405 host target gene. LOC92017 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92017 BINDING SITE, designated SEQ ID:33707, to the nucleotide sequence of VGAM405 RNA, herein designated VGAM RNA, also designated SEQ ID:3116.

[19621] Another function of VGAM405 is therefore inhibition of LOC92017 (Accession XM\_042234). Accordingly, utilities of VGAM405 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92017. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 406 (VGAM406) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[19622] VGAM406 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM406 was detected is described hereinabove with reference to Figs. 1–8.

[19623] VGAM406 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cryphonectria Hypovirus 1. VGAM406 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19624] VGAM406 gene encodes a VGAM406 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM406 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM406 precursor RNA is designated SEQ ID:392, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:392 is located at position 3878 relative to the genome of Cryphonectria Hypovirus 1.

[19625] VGAM406 precursor RNA folds onto itself, forming VGAM406 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[19626] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM406 folded precursor RNA into VGAM406 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 55%) nucleotide se-  
quence of VGAM406 RNA is designated SEQ ID:3117, and  
is provided hereinbelow with reference to the sequence  
listing part.

[19627] VGAM406 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM406 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM406 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[19628] VGAM406 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM406 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM406 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM406 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM406 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[19629] The complementary binding of VGAM406 RNA, herein designated VGAM RNA, to host target binding sites on VGAM406 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM406 host target RNA into VGAM406 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19630] It is appreciated that VGAM406 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM406 host target genes. The mRNA of each one of this plurality of VGAM406 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM406 RNA, herein designated VGAM RNA, and which when bound by VGAM406 RNA causes inhibition of translation of respective one or more VGAM406 host target proteins.

[19631] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM406 gene, herein designated VGAM GENE, on one or

more VGAM406 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19632] It is yet further appreciated that a function of VGAM406 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of viral infection by Cryphonectria Hypovirus 1. Specific functions, and accordingly utilities, of VGAM406 correlate with, and may be deduced from, the identity of the host target genes which VGAM406 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [19633] Nucleotide sequences of the VGAM406 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM406 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM406 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM406 are further described hereinbelow with reference to Table 1.
- [19634] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM406 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM406 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19635] As mentioned hereinabove with reference to Fig. 1, a function of VGAM406 gene, herein designated VGAM is inhibition of expression of VGAM406 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM406 correlate with, and may be deduced from, the identity of the target genes which VGAM406 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [19636] Deleted In Lung and Esophageal Cancer 1 (DLEC1, Acces-



sion NM\_007338) is a VGAM406 host target gene. DLEC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DLEC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLEC1 BINDING SITE, designated SEQ ID:14270, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19637] A function of VGAM406 is therefore inhibition of Deleted In Lung and Esophageal Cancer 1 (DLEC1, Accession NM\_007338). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLEC1. Estrogen-related Receptor Beta (ESRRB, Accession XM\_041087) is another VGAM406 host target gene. ESRRB BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ESRRB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRB BINDING SITE, designated SEQ ID:33438, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3117.

[19638] Another function of VGAM406 is therefore inhibition of Estrogen-related Receptor Beta (ESRRB, Accession XM\_041087), a gene which Estrogen-related receptor beta; member of the nuclear hormone receptor family. Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESRRB. The function of ESRRB has been established by previous studies. See estrogen-related receptor-alpha (ESRRA; 601998). Giguere et al. (1988) first identified ESRRB as a gene whose product is similar to the estrogen receptor (OMIM Ref. No. 133430). Sladek et al. (1997) mapped ESRRB to 14q24.3 by fluorescence in situ hybridization. Luo et al. (1997) demonstrated that mouse *Esrrb* plays an essential role in placental development: homozygous null *Esrrb* mutants die in midgestation due to abnormal development of the chorion and defective diploid trophoblast proliferation. Its embryonic lethal phenotype prevented the identification of potential roles for ESRRB in postnatal physiology.

[19639] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [19640] Luo, J.; Sladek, R.; Bader, J. A.; Matthyssen, A.; Rossant, J.; Giguere, V. : Placental abnormalities in mouse embryos lacking orphan nuclear receptor ERR-beta. Nature 388: 778-782, 1997. ; and
- [19641] Sladek, R.; Beatty, B.; Squire, J.; Copeland, N. G.; Gilbert, D. J.; Jenkins, N. A.; Giguere, V. : Chromosomal mapping of the human and murine orphan receptors ERR-alpha (ESRRA) and ERR.
- [19642] Further studies establishing the function and utilities of ESRRB are found in John Hopkins OMIM database record ID 602167, and in cited publications numbered 94 and 6348 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Kruppel-like Factor 4 (gut) (KLF4, Accession NM\_004235) is another VGAM406 host target gene. KLF4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KLF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KLF4 BINDING SITE, designated SEQ ID:10429, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19643] Another function of VGAM406 is therefore inhibition of Kruppel-like Factor 4 (gut) (KLF4, Accession NM\_004235), a gene which may be involved in the differentiation of epithelial cells and may also function in the development of the skeleton and kidney. Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KLF4. The function of KLF4 has been established by previous studies. Shields et al. (1996) cloned a mouse cDNA, which they named gut-enriched Kruppel-like factor (Gklf), that encodes a member of the Kruppel family of transcription factors. Immunofluorescence revealed that Gklf is localized to the nucleus and is found at highest levels in growth-arrested cells. Shields et al. (1996) found that transfection of Gklf into COS-1 cells causes an inhibition of DNA synthesis. In the mouse, the authors found that Gklf mRNA is most abundant in the colon and is also expressed in the testis, lung, and small intestine. Garrett-Sinha et al. (1996) identified a novel zinc finger protein whose mRNA is expressed at high levels in the epidermal layer of the skin and in epithelial cells in the tongue, palate, esophagus, stomach, and colon of newborn mice. They named the protein EZF for 'epithelial zinc finger.' By

screening a human umbilical vein endothelial cell cDNA library with a cDNA encoding the C-terminal zinc finger region of EKLF (KLF1; 600599), Yet et al. (1998) isolated a cDNA encoding KLF4, which they called EZF. The predicted 470-amino acid KLF4 protein has a proline- and serine-rich N terminus and contains 3 C<sub>2</sub>H<sub>2</sub> Kruppel-type zinc fingers at the C terminus. KLF4 also contains a potential nuclear localization signal. The human KLF4 protein shares 91% sequence identity with mouse Ezf. Recombinant KLF4 bound specifically to a probe containing the CACCC core sequence in gel mobility shift assays. In contrast to other members of the EKLF family, which are transcriptional activators, KLF4 functioned as a transcriptional repressor in transient transfection studies. The authors identified both the repression domain and the activation domain within KLF4. Northern blot analysis detected a 3.5-kb KLF4 transcript in RNA from both human umbilical vein endothelial cells and human aortic endothelial cells. By radiation hybrid mapping, Yet et al. (1998) mapped the human KLF4 gene to 9q31. Garrett-Sinha et al. (1996) mapped the mouse EZF gene to chromosome 4, in close proximity to the thioredoxin gene (OMIM Ref. No. 187700). Animal model experiments lend further support

to the function of KLF4. Located at the interface between body and environment, the epidermis must protect the body against toxic agents and dehydration, and protect itself against physical and mechanical stresses. Acquired just before birth and at the last stage of epidermal differentiation, the skin's proteinaceous/lipid barrier creates a surface seal essential for protecting animals against microbial infections and dehydration. Segre et al. (1999) showed that Kruppel-like factor-4 (KLF4), highly expressed in the differentiating layers of epidermis, is both vital to and selective for barrier acquisition. *Klf4*  $-/-$  mice die shortly after birth due to loss of skin barrier function, as measured by penetration of external dyes and rapid loss of body fluids. The defect was not corrected by grafting of *Klf4*  $-/-$  skin onto nude mice. Loss of the barrier occurred without morphologic or biochemical alterations to the well-known structural features of epidermis that are essential for mechanical integrity. Instead, late-stage differentiation structures were selectively perturbed, including the cornified envelope, a likely scaffold for lipid organization. Using suppressive hybridization, Segre et al. (1999) identified 3 transcripts encoding cornified envelope proteins with altered expression in the absence of

Klf4. Sprr2a (OMIM Ref. No. 182267) was one, this being the only epidermal gene whose promoter is known to possess a functional Klf4 binding site. These studies provide a new insight into transcriptional governance of barrier function, and pave the way for unraveling the molecular events that orchestrate this essential process

[19644] It is appreciated that the abovementioned animal model for KLF4 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[19645] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19646] Garrett-Sinha, L. A.; Eberspaecher, H.; Seldin, M. F.; de Crombrughe, B. : A gene for a novel zinc-finger protein expressed in differentiated epithelial cells and transiently in certain mesenchymal cells. J. Biol. Chem. 271: 31384–31390, 1996. ; and

[19647] Segre, J. A.; Bauer, C.; Fuchs, E. : Klf4 is a transcription factor required for establishing the barrier function of the skin. Nature Genet. 22: 356–360, 1999.

[19648] Further studies establishing the function and utilities of KLF4 are found in John Hopkins OMIM database record ID

602253, and in cited publications numbered 926–929 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neurotensin Receptor 1 (high affinity) (NTSR1, Accession NM\_002531) is another VGAM406 host target gene. NTSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NTSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NTSR1 BINDING SITE, designated SEQ ID:8367, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19649] Another function of VGAM406 is therefore inhibition of Neurotensin Receptor 1 (high affinity) (NTSR1, Accession NM\_002531), a gene which is associated with G proteins that activate a phosphatidylinositol–calcium second messenger system. Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NTSR1. The function of NTSR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to



VGAM200.Phospholipase A2, Group IID (PLA2G2D, Accession NM\_012400) is another VGAM406 host target gene. PLA2G2D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLA2G2D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLA2G2D BINDING SITE, designated SEQ ID:14768, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19650] Another function of VGAM406 is therefore inhibition of Phospholipase A2, Group IID (PLA2G2D, Accession NM\_012400), a gene which is involved in phospholipid digestion, remodeling of cell membranes, and host defense, as well as pathophysiologic processes. Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLA2G2D. The function of PLA2G2D and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74.Recombination Activating Gene 2 (RAG2, Accession XM\_089839) is another VGAM406

host target gene. RAG2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAG2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAG2 BINDING SITE, designated SEQ ID:39987, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19651] Another function of VGAM406 is therefore inhibition of Recombination Activating Gene 2 (RAG2, Accession XM\_089839). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAG2. SORCS2 (Accession NM\_020777) is another VGAM406 host target gene. SORCS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SORCS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SORCS2 BINDING SITE, designated SEQ ID:21874, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ

ID:3117.

[19652] Another function of VGAM406 is therefore inhibition of SORCS2 (Accession NM\_020777). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORCS2. TEM5 (Accession NM\_032777) is another VGAM406 host target gene. TEM5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TEM5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TEM5 BINDING SITE, designated SEQ ID:26520, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19653] Another function of VGAM406 is therefore inhibition of TEM5 (Accession NM\_032777), a gene which involves in development of midline glia and commissural axon pathways. Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TEM5. The function of TEM5 has been established by previous studies. Using serial analysis of gene expression (SAGE), St Croix et al. (2000) identified

partial cDNAs corresponding to several tumor endothelial markers (TEMs) that displayed elevated expression during tumor angiogenesis. Among the genes they identified was TEM5. Using database searches and 5-prime RACE, Carson-Walter et al. (2001) derived sequences covering the entire TEM5 coding region, which encodes a predicted 7-pass transmembrane protein of 1,331 amino acids. The N-terminal extracellular region contains 4 simple leucine-rich repeats (LRRs), a C-terminal LRR, an immunoglobulin-type domain, a hormone receptor domain, and a putative G protein-coupled receptor (GPCR) proteolysis site domain typical of class II family members and required for endogenous proteolysis. Based on sequence analysis and hydrophobicity plots, Carson-Walter et al. (2001) hypothesized that TEM5 may be a member of the GPCR superfamily involved in transmitting signals across the cell membrane. The mouse ortholog of TEM5 shares 87% amino acid identity with the human protein. In situ hybridization analysis of human colorectal cancer by Carson-Walter et al. (2001) revealed that TEM5 was expressed clearly in the endothelial cells of the tumor stroma but not in the endothelial cells of normal colonic tissue. The authors used in situ hybridization to examine

Tem5 expression in murine tumors, embryos, and adult tissues. They detected Tem5 in the vasculature of developing embryonic liver and brain as well as in the vessels of transplanted syngeneic and human tumors. In various normal adult mouse tissues, Carson-Walter et al. (2001) detected weak Tem5 expression only in a small fraction of the vessels of brain, heart, intestine, lung, skeletal muscle, and pancreas.

[19654] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19655] Carson-Walter, E. B.; Watkins, D. N.; Nanda, A.; Vogelstein, B.; Kinzler, K. W.; St. Croix, B. : Cell surface tumor endothelial markers are conserved in mice and humans. Cancer Res. 61: 6649-6655, 2001. ; and

[19656] St. Croix, B.; Rago, C.; Velculescu, V.; Traverso, G.; Romans, K. E.; Montgomery, E.; Lal, A.; Riggins, G. J.; Lengauer, C.; Vogelstein, B.; Kinzler, K. W. : Genes expressed in human tu.

[19657] Further studies establishing the function and utilities of TEM5 are found in John Hopkins OMIM database record ID 606823, and in cited publications numbered 689 and 6907 listed in the bibliography section hereinbelow, which

are also hereby incorporated by reference.UDP-Gal:betaGlcNAc Beta 1,3-galactosyltransferase, Polypeptide 1 (B3GALT1, Accession NM\_020981) is another VGAM406 host target gene. B3GALT1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by B3GALT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B3GALT1 BINDING SITE, designated SEQ ID:21972, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19658] Another function of VGAM406 is therefore inhibition of UDP-Gal:betaGlcNAc Beta 1,3-galactosyltransferase, Polypeptide 1 (B3GALT1, Accession NM\_020981). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B3GALT1. FLJ23816 (Accession NM\_144655) is another VGAM406 host target gene. FLJ23816 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ23816, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of FLJ23816 BINDING SITE, designated SEQ ID:29478, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19659] Another function of VGAM406 is therefore inhibition of FLJ23816 (Accession NM\_144655). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23816. FLJ31737 (Accession NM\_144984) is another VGAM406 host target gene. FLJ31737 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ31737, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ31737 BINDING SITE, designated SEQ ID:29589, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19660] Another function of VGAM406 is therefore inhibition of FLJ31737 (Accession NM\_144984). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ31737. GLTP (Accession NM\_016433) is another VGAM406 host

target gene. GLTP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLTP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLTP BINDING SITE, designated SEQ ID:18556, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19661] Another function of VGAM406 is therefore inhibition of GLTP (Accession NM\_016433). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLTP. KIAA0828 (Accession XM\_088105) is another VGAM406 host target gene. KIAA0828 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0828, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0828 BINDING SITE, designated SEQ ID:39515, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.



[19662] Another function of VGAM406 is therefore inhibition of KIAA0828 (Accession XM\_088105). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0828. Pleiomorphic Adenoma Gene-like 2 (PLAGL2, Accession XM\_047007) is another VGAM406 host target gene. PLAGL2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PLAGL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLAGL2 BINDING SITE, designated SEQ ID:34875, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19663] Another function of VGAM406 is therefore inhibition of Pleiomorphic Adenoma Gene-like 2 (PLAGL2, Accession XM\_047007). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLAGL2. RASD Family, Member 2 (RASD2, Accession NM\_014310) is another VGAM406 host target gene. RASD2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by RASD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASD2 BINDING SITE, designated SEQ ID:15607, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19664] Another function of VGAM406 is therefore inhibition of RASD Family, Member 2 (RASD2, Accession NM\_014310). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASD2. LOC200205 (Accession XM\_114152) is another VGAM406 host target gene. LOC200205 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200205, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200205 BINDING SITE, designated SEQ ID:42737, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19665] Another function of VGAM406 is therefore inhibition of

LOC200205 (Accession XM\_114152). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200205. LOC204084 (Accession XM\_115181) is another VGAM406 host target gene. LOC204084 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC204084, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC204084 BINDING SITE, designated SEQ ID:43084, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19666] Another function of VGAM406 is therefore inhibition of LOC204084 (Accession XM\_115181). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC204084. LOC221632 (Accession XM\_168117) is another VGAM406 host target gene. LOC221632 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221632, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC221632 BINDING SITE, designated SEQ ID:45036, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19667] Another function of VGAM406 is therefore inhibition of LOC221632 (Accession XM\_168117). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221632. LOC90768 (Accession XM\_033986) is another VGAM406 host target gene. LOC90768 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90768, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90768 BINDING SITE, designated SEQ ID:31985, to the nucleotide sequence of VGAM406 RNA, herein designated VGAM RNA, also designated SEQ ID:3117.

[19668] Another function of VGAM406 is therefore inhibition of LOC90768 (Accession XM\_033986). Accordingly, utilities of VGAM406 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90768. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 407 (VGAM407) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19669] VGAM407 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM407 was detected is described hereinabove with reference to Figs. 1–8.

[19670] VGAM407 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Melon Necrotic Spot Virus. VGAM407 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19671] VGAM407 gene encodes a VGAM407 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM407 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM407 precursor RNA is designated SEQ ID:393, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:393 is

located at position 1162 relative to the genome of Melon Necrotic Spot Virus.

[19672] VGAM407 precursor RNA folds onto itself, forming VGAM407 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19673] An enzyme complex designated DICER COMPLEX, `dices` the VGAM407 folded precursor RNA into VGAM407 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM407 RNA is designated SEQ ID:3118, and is provided hereinbelow with reference to the sequence listing part.

[19674] VGAM407 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM407 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM407 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[19675] VGAM407 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM407 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM407 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM407 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM407 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[19676] The complementary binding of VGAM407 RNA, herein designated VGAM RNA, to host target binding sites on VGAM407 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM407 host target RNA into VGAM407 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19677] It is appreciated that VGAM407 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM407 host target genes. The mRNA of each one of this plurality of VGAM407 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM407 RNA, herein designated VGAM RNA, and which when bound by VGAM407 RNA causes inhibition of translation of respective one or more VGAM407



host target proteins.

[19678] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM407 gene, herein designated VGAM GENE, on one or more VGAM407 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19679] It is yet further appreciated that a function of VGAM407 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment of viral infection by Melon Necrotic Spot Virus.

Specific functions, and accordingly utilities, of VGAM407 correlate with, and may be deduced from, the identity of the host target genes which VGAM407 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19680] Nucleotide sequences of the VGAM407 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM407 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM407 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM407 are further described hereinbelow with reference to Table 1.

[19681] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM407 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM407 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19682] As mentioned hereinabove with reference to Fig. 1, a function of VGAM407 gene, herein designated VGAM is inhibition of expression of VGAM407 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM407 correlate with, and may be deduced from, the identity of the target genes which VGAM407 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19683] Paired Box Gene 2 (PAX2, Accession NM\_003987) is a VGAM407 host target gene. PAX2 BINDING SITE1 and PAX2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PAX2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAX2 BINDING SITE1 and PAX2 BINDING SITE2, designated SEQ ID:10137 and SEQ ID:10143 respectively, to the nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19684] A function of VGAM407 is therefore inhibition of Paired Box Gene 2 (PAX2, Accession NM\_003987), a gene which involves in kidney cell differentiation. Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAX2. The function of PAX2 has been established by previous studies. Sanyanusin et al. (1996) obtained the complete genomic structure of the human PAX2 gene. They de-

scribed 5 genomic lambda clones containing human PAX2 gene sequences, 4 of which had previously been reported by them (Sanyanusin et al., 1995). The fifth clone, which included exons 7 and 8, was obtained by Sanyanusin et al. (1996) from a subgenomic lambda cDNA library of size-fractionated EcoRI fragments ranging in size from 6 to 8 kb. Sequencing and restriction mapping of these clones showed that the human PAX2 gene is composed of 12 exons spanning approximately 70 kb. They also found 2 alternatively spliced exons corresponding to exon 10 (Ward et al., 1994) and a 69-bp inserted sequence that they designated as exon 6. The 69-bp insert is homologous to a 69-bp insert reported in the murine Pax2 gene by Dressler et al. (1990). Sanyanusin et al. (1996) identified a (CA)<sub>n</sub> dinucleotide repeat polymorphism in PAX2 which they mapped immediately upstream of exon 9. The PAX2 gene is expressed in primitive cells of the kidney, ureter, eye, ear, and central nervous system. Based on the known expression pattern of PAX2, Sanyanusin et al. (1995) predicted that the phenotype caused by mutations of PAX2 would probably consist of autosomal dominant eye malformations, sensorineural hearing loss, and renal hypoplasia. Pursuing this suspicion, they found deletion of a

single nucleotide in exon 5 of the PAX2 gene (167409.0001) in a father and 3 of his 5 sons who had optic nerve colobomas, renal hypoplasia, mild proteinuria, and vesicoureteral reflux. The nucleotide deletion caused a frameshift in the conserved octapeptide sequence. The phenotype was similar to that of Krd mutant mice which lack a portion of chromosome 19 that is homologous to human 10q24 and includes the Pax2 gene. These mice have reduced thickness of the renal cortex, a reduced number of glomeruli at birth, and reduced amplitudes on electroretinogram. In the Krd mouse, the deletion of chromosome 19 was transgene-induced (Keller et al., 1994). Coloboma of the optic nerve with renal disease (OMIM Ref. No. 120330) is a recognized syndrome. Renal dysplasia and retinal aplasia are combined in the Loken-Senior syndrome (OMIM Ref. No. 266900). Ocular abnormalities occur also with familial juvenile nephronophthisis (OMIM Ref. No. 256100), but that disorder maps to chromosome 2. Animal model experiments lend further support to the function of PAX2. To determine the direct effects of PAX2 mutations on kidney development, fetal kidneys of mice carrying a Pax2(1Neu) mutation were examined. At embryonic day 15 (E15), heterozygous mutant kidneys were

approximately 60% the size of those of wildtype littermates, and the number of nephrons was strikingly reduced. Heterozygous mutant mice showed increased apoptotic cell death during fetal kidney development, but the increased apoptosis was not associated with random stochastic inactivation of Pax2 expression in mutant kidneys; Pax2 was shown to be biallelically expressed during kidney development. The findings supported the conclusion that heterozygous mutations of the PAX2 gene are associated with increased apoptosis and reduced branching of the ureteric bud, due to reduced PAX2 dosage during a critical window in kidney development.

[19685] It is appreciated that the abovementioned animal model for PAX2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[19686] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19687] Sanyanusin, P.; Schimmenti, L. A.; McNoe, L. A.; Ward, T. A.; Pierpont, M. E. M.; Sullivan, M. J.; Dobyns, W. B.; Eccles, M. R. : Mutation of the PAX2 gene in a family with optic nerve colobomas, renal anomalies and vesicoureteral re-

flux. Nature Genet. 9: 358–364, 1995. ; and

[19688] Porteous, S.; Torban, E.; Cho, N.-P.; Cunliffe, H.; Chua, L.; McNoe, L.; Ward, T.; Souza, C.; Gus, P.; Giugliani, R.; Sato, T.; Yun, K.; Favor, J.; Sicotte, M.; Goodyer, P.; Eccles, M.

[19689] Further studies establishing the function and utilities of PAX2 are found in John Hopkins OMIM database record ID 167409, and in cited publications numbered 10331–10334, 10339–10338, 593 and 10708–10718 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0397 (Accession XM\_029438) is another VGAM407 host target gene. KIAA0397 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA0397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0397 BINDING SITE, designated SEQ ID:30895, to the nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19690] Another function of VGAM407 is therefore inhibition of KIAA0397 (Accession XM\_029438). Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0397. KIAA1036 (Accession NM\_014909) is another VGAM407 host target gene. KIAA1036 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1036, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1036 BINDING SITE, designated SEQ ID:17123, to the nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19691] Another function of VGAM407 is therefore inhibition of KIAA1036 (Accession NM\_014909). Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1036. Mitogen-activated Protein Kinase 8 Interacting Protein 2 (MAPK8IP2, Accession NM\_016431) is another VGAM407 host target gene. MAPK8IP2 BINDING SITE1 through MAPK8IP2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MAPK8IP2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-



cleotide sequences of MAPK8IP2 BINDING SITE1 through MAPK8IP2 BINDING SITE3, designated SEQ ID:18551, SEQ ID:14703 and SEQ ID:29154 respectively, to the nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19692] Another function of VGAM407 is therefore inhibition of Mitogen-activated Protein Kinase 8 Interacting Protein 2 (MAPK8IP2, Accession NM\_016431). Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPK8IP2. LOC159121 (Accession XM\_099028) is another VGAM407 host target gene. LOC159121 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC159121, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC159121 BINDING SITE, designated SEQ ID:42066, to the nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19693] Another function of VGAM407 is therefore inhibition of LOC159121 (Accession XM\_099028). Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC159121. LOC163682 (Accession XM\_099402) is another VGAM407 host target gene. LOC163682 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163682, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163682 BINDING SITE, designated SEQ ID:42099, to the nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19694] Another function of VGAM407 is therefore inhibition of LOC163682 (Accession XM\_099402). Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163682. LOC51068 (Accession NM\_015938) is another VGAM407 host target gene. LOC51068 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51068, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51068 BINDING SITE, designated SEQ ID:18059, to the

nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19695] Another function of VGAM407 is therefore inhibition of LOC51068 (Accession NM\_015938). Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51068. LOC92335 (Accession XM\_044379) is another VGAM407 host target gene. LOC92335 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92335, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92335 BINDING SITE, designated SEQ ID:34192, to the nucleotide sequence of VGAM407 RNA, herein designated VGAM RNA, also designated SEQ ID:3118.

[19696] Another function of VGAM407 is therefore inhibition of LOC92335 (Accession XM\_044379). Accordingly, utilities of VGAM407 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92335. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 408 (VGAM408) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19697] VGAM408 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM408 was detected is described hereinabove with reference to Figs. 1–8.

[19698] VGAM408 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Melon Necrotic Spot Virus. VGAM408 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19699] VGAM408 gene encodes a VGAM408 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM408 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM408 precursor RNA is designated SEQ ID:394, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:394 is located at position 266 relative to the genome of Melon Necrotic Spot Virus.

[19700] VGAM408 precursor RNA folds onto itself, forming VGAM408 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19701] An enzyme complex designated DICER COMPLEX, `dices` the VGAM408 folded precursor RNA into VGAM408 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM408 RNA is designated SEQ ID:3119, and is provided hereinbelow with reference to the sequence listing part.

[19702] VGAM408 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM408 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM408 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19703] VGAM408 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM408 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM408 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM408 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM408 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19704] The complementary binding of VGAM408 RNA, herein designated VGAM RNA, to host target binding sites on VGAM408 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM408 host target RNA into VGAM408 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19705] It is appreciated that VGAM408 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM408 host target genes. The mRNA of each one of this plurality of VGAM408 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM408 RNA, herein designated VGAM RNA, and which when bound by VGAM408 RNA causes inhibition of translation of respective one or more VGAM408 host target proteins.

[19706] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM408 gene, herein designated VGAM GENE, on one or more VGAM408 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19707] It is yet further appreciated that a function of VGAM408 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM408 include diagnosis, prevention and treatment of viral infection by Melon Necrotic Spot Virus. Specific functions, and accordingly utilities, of VGAM408 correlate with, and may be deduced from, the identity of



the host target genes which VGAM408 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [19708] Nucleotide sequences of the VGAM408 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM408 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM408 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM408 are further described hereinbelow with reference to Table 1.
- [19709] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM408 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM408 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19710] As mentioned hereinabove with reference to Fig. 1, a function of VGAM408 gene, herein designated VGAM is inhibition of expression of VGAM408 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM408 correlate with, and may be deduced from, the identity of the target genes which VGAM408

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19711] A Kinase (PRKA) Anchor Protein 6 (AKAP6, Accession NM\_004274) is a VGAM408 host target gene. AKAP6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AKAP6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP6 BINDING SITE, designated SEQ ID:10488, to the nucleotide sequence of VGAM408 RNA, herein designated VGAM RNA, also designated SEQ ID:3119.

[19712] A function of VGAM408 is therefore inhibition of A Kinase (PRKA) Anchor Protein 6 (AKAP6, Accession NM\_004274). Accordingly, utilities of VGAM408 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP6. Rho Guanine Nucleotide Exchange Factor (GEF) 11 (ARHGEF11, Accession NM\_014784) is another VGAM408 host target gene. ARHGEF11 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ARHGEF11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of ARHGEF11 BINDING SITE, designated SEQ ID:16638, to the nucleotide sequence of VGAM408 RNA, herein designated VGAM RNA, also designated SEQ ID:3119.

[19713] Another function of VGAM408 is therefore inhibition of Rho Guanine Nucleotide Exchange Factor (GEF) 11 (ARHGEF11, Accession NM\_014784). Accordingly, utilities of VGAM408 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGEF11. LOC149157 (Accession XM\_086442) is another VGAM408 host target gene. LOC149157 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149157, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149157 BINDING SITE, designated SEQ ID:38657, to the nucleotide sequence of VGAM408 RNA, herein designated VGAM RNA, also designated SEQ ID:3119.

[19714] Another function of VGAM408 is therefore inhibition of LOC149157 (Accession XM\_086442). Accordingly, utilities of VGAM408 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC149157. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 409 (VGAM409) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19715] VGAM409 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM409 was detected is described hereinabove with reference to Figs. 1–8.

[19716] VGAM409 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Melon Necrotic Spot Virus. VGAM409 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19717] VGAM409 gene encodes a VGAM409 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM409 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM409 precursor RNA is designated SEQ ID:395, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:395 is located at position 894 relative to the genome of Melon Necrotic Spot Virus.

[19718] VGAM409 precursor RNA folds onto itself, forming VGAM409 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19719] An enzyme complex designated DICER COMPLEX, `dices` the VGAM409 folded precursor RNA into VGAM409 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 49%) nucleotide sequence of VGAM409 RNA is designated SEQ ID:3120, and is provided hereinbelow with reference to the sequence listing part.

[19720] VGAM409 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM409 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM409 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19721] VGAM409 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM409 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM409 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM409 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM409 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[19722] The complementary binding of VGAM409 RNA, herein designated VGAM RNA, to host target binding sites on VGAM409 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM409 host target RNA into VGAM409 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19723] It is appreciated that VGAM409 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM409 host target genes. The mRNA of each one of this plurality of VGAM409 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM409 RNA, herein designated VGAM RNA, and which when bound by VGAM409 RNA causes in-

hibition of translation of respective one or more VGAM409 host target proteins.

[19724] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM409 gene, herein designated VGAM GENE, on one or more VGAM409 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19725] It is yet further appreciated that a function of VGAM409 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM409 include diagnosis, prevention and



treatment of viral infection by Melon Necrotic Spot Virus. Specific functions, and accordingly utilities, of VGAM409 correlate with, and may be deduced from, the identity of the host target genes which VGAM409 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [19726] Nucleotide sequences of the VGAM409 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM409 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM409 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM409 are further described hereinbelow with reference to Table 1.
- [19727] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM409 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM409 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19728] As mentioned hereinabove with reference to Fig. 1, a function of VGAM409 gene, herein designated VGAM is inhibition of expression of VGAM409 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM409 correlate with, and may be deduced from, the identity of the target genes which VGAM409 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19729] FCRH1 (Accession NM\_052938) is a VGAM409 host target gene. FCRH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FCRH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FCRH1 BINDING SITE, designated SEQ ID:27498, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19730] A function of VGAM409 is therefore inhibition of FCRH1 (Accession NM\_052938). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FCRH1. SRY (sex determining region Y)-box 4 (SOX4, Accession NM\_003107) is another VGAM409 host target gene. SOX4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SOX4, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOX4 BINDING SITE, designated SEQ ID:9073, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19731] Another function of VGAM409 is therefore inhibition of SRY (sex determining region Y)-box 4 (SOX4, Accession NM\_003107), a gene which binds with high affinity to the t-cell enhancer motif 5'-aacaag-3' motif. Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOX4. The function of SOX4 has been established by previous studies. SOX4 from both human and mouse was shown by van de Wetering et al. (1993) to be expressed primarily in T and pre-B lymphocyte cell lines. They also showed that the mouse Sox4 protein binds with high affinity to the (A/T)(A/T)CAAAG motif found in several T-cell specific enhancers. By transient expression of chimeric Sox4 constructs, van de Wetering et al. (1993) showed that Sox4 has separable DNA-binding and trans-activation domains. The authors concluded that SOX4 is a lymphocyte-specific transcriptional activator. Using a

yeast 2-hybrid screen, Geijsen et al. (2001) identified the mouse transcriptional factor Sox4 as a binding partner for syntenin (SDCBP; 602217) but not for interleukin-5 receptor-alpha (IL5RA; 147851), which interacts with the PDZ domains of syntenin. The syntenin-Sox4 interaction occurs outside of the PDZ domains of syntenin. Luciferase reporter analysis and fluorescence microscopy showed that IL5 (OMIM Ref. No. 147850), but not IL3 (OMIM Ref. No. 147740), induces cytoplasmic and nuclear expression of syntenin and, in a syntenin- and cytoplasmic IL5RA-dependent manner, of Sox4. Geijsen et al. (2001) concluded that syntenin acts as an adaptor molecule in the IL5RA-mediated activation of SOX4. They also noted that mice lacking either Il5ra or Sox4 have defects in B-cell development

[19732] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19733] Geijsen, N.; Uings, I. J.; Pals, C.; Armstrong, J.; McKinnon, M.; Raaijmakers, J. A. M.; Lammers, J.-W. J.; Koenderman, L.; Coffey, P. J. : Cytokine-specific transcriptional regulation through an IL-5R-alpha interacting protein. Science 293: 1136-1138, 2001. ; and

[19734] Suzuki, T.; Shen, H.; Akagi, K.; Morse, H. C., III; Malley, J. D.; Naiman, D. Q.; Jenkins, N. A.; Copeland, N. G. : New genes involved in cancer identified by retroviral tagging. Nature.

[19735] Further studies establishing the function and utilities of SOX4 are found in John Hopkins OMIM database record ID 184430, and in cited publications numbered 12406–12408, 346 and 12409–12413 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Timeless Homolog (Drosophila) (TIMELESS, Accession NM\_003920) is another VGAM409 host target gene. TIMELESS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIMELESS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMELESS BINDING SITE, designated SEQ ID:10005, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19736] Another function of VGAM409 is therefore inhibition of Timeless Homolog (Drosophila) (TIMELESS, Accession NM\_003920), a gene which involves in circadian oscilla-

tion autoregulation. Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIMELESS. The function of TIMELESS has been established by previous studies. Cellular pacemakers located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus control circadian rhythms. In *Drosophila*, a central clock mechanism involves the dynamic regulation of 2 genes, 'period' (per; OMIM Ref. No. 602260) and 'timeless' (tim), which physically interact and participate in an intracellular transcriptional/translational feedback loop. The transcription of per and tim is positively regulated by the Clock (OMIM Ref. No. 601851) and BMAL1 (OMIM Ref. No. 602550) proteins, which form heterodimers. By searching EST databases, Sangoram et al. (1998), Zylka et al. (1998), and Koike et al. (1998) identified cDNAs corresponding to human (TIM) and mouse (Tim) homologs of *Drosophila* timeless. Sangoram et al. (1998) reported that the predicted 1,208-amino acid human protein is 84% identical to mouse Tim. The mammalian proteins share 4 regions of homology with *Drosophila* tim, including regions involved in nuclear localization, protein-protein interaction with PER, and cytoplasmic localization. Northern blot analysis

revealed that TIM was expressed as a 4.5-kb mRNA in all human tissues tested, with the highest levels in placenta, pancreas, thymus, and testis. In situ hybridization indicated that unlike those of *Drosophila*, mouse Tim transcript levels do not oscillate in the SCN or in the retina. Sangoram et al. (1998) demonstrated that human TIM interacts with *Drosophila* per, mouse PER1, and mouse PER2 (see OMIM Ref. No. 603426) in vitro. When expressed in *Drosophila* cells, TIM mimicked a *Drosophila* tim cellular function by interacting with *Drosophila* per and translocating into the nucleus. In addition, when expressed in mammalian cells, human TIM and mouse PER1 specifically inhibited CLOCK-BMAL1-induced transactivation of the mouse PER1 promoter. These authors concluded that TIM and Tim are the mammalian orthologs of *Drosophila* tim. In contrast, Zylka et al. (1998) were unable to detect mouse Per-Tim interactions in yeast 2-hybrid assays. They found an array of interactions between the various mouse Per proteins, and suggested that Per-Per interactions have replaced the function of Per-Tim dimers in the molecular workings of the mammalian circadian clock.

[19737] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [19738] Sangoram, A. M.; Saez, L.; Antoch, M. P.; Gekakis, N.; Staknis, D.; Whiteley, A.; Fruechte, E. M.; Vitaterna, M. H.; Shimomura, K.; King, D. P.; Young, M. W.; Weitz, C. J.; Takahashi, J. S. : Mammalian circadian autoregulatory loop: a timeless ortholog and mPer1 interact and negatively regulate CLOCK-BMAL1-induced transcription. *Neuron* 21: 1101-1113, 1998. ; and
- [19739] Zylka, M. J.; Shearman, L. P.; Levine, J. D.; Jin, X.; Weaver, D. R.; Reppert, S. M. : Molecular analysis of mammalian timeless. *Neuron* 21: 1115-1122, 1998.
- [19740] Further studies establishing the function and utilities of TIMELESS are found in John Hopkins OMIM database record ID 603887, and in cited publications numbered 7627-7629 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ10508 (Accession NM\_018118) is another VGAM409 host target gene. FLJ10508 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10508, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10508 BINDING SITE, designated



SEQ ID:19889, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19741] Another function of VGAM409 is therefore inhibition of FLJ10508 (Accession NM\_018118). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10508. FLJ10724 (Accession NM\_018194) is another VGAM409 host target gene. FLJ10724 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10724, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10724 BINDING SITE, designated SEQ ID:20054, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19742] Another function of VGAM409 is therefore inhibition of FLJ10724 (Accession NM\_018194). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10724. FLJ11320 (Accession NM\_018389) is another VGAM409 host target gene. FLJ11320 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ11320, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11320 BINDING SITE, designated SEQ ID:20425, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19743] Another function of VGAM409 is therefore inhibition of FLJ11320 (Accession NM\_018389). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11320. FLJ13912 (Accession NM\_022770) is another VGAM409 host target gene. FLJ13912 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13912, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13912 BINDING SITE, designated SEQ ID:23026, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19744] Another function of VGAM409 is therefore inhibition of

FLJ13912 (Accession NM\_022770). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13912. FLJ32356 (Accession NM\_144671) is another VGAM409 host target gene. FLJ32356 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ32356, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32356 BINDING SITE, designated SEQ ID:29492, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19745] Another function of VGAM409 is therefore inhibition of FLJ32356 (Accession NM\_144671). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32356. Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230) is another VGAM409 host target gene. NUDT11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUDT11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUDT11 BINDING SITE, designated SEQ ID:30139, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19746] Another function of VGAM409 is therefore inhibition of Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUDT11. LOC256997 (Accession XM\_170900) is another VGAM409 host target gene. LOC256997 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256997, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256997 BINDING SITE, designated SEQ ID:45651, to the nucleotide sequence of VGAM409 RNA, herein designated VGAM RNA, also designated SEQ ID:3120.

[19747] Another function of VGAM409 is therefore inhibition of LOC256997 (Accession XM\_170900). Accordingly, utilities of VGAM409 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC256997. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 410 (VGAM410) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19748] VGAM410 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM410 was detected is described hereinabove with reference to Figs. 1–8.

[19749] VGAM410 gene, herein designated VGAM GENE, is a viral gene contained in the genome of O'nyong–nyong Virus. VGAM410 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19750] VGAM410 gene encodes a VGAM410 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM410 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM410 precursor RNA is designated SEQ

ID:396, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:396 is located at position 5873 relative to the genome of O'nyong-nyong Virus.

[19751] VGAM410 precursor RNA folds onto itself, forming VGAM410 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19752] An enzyme complex designated DICER COMPLEX, `dices` the VGAM410 folded precursor RNA into VGAM410 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM410 RNA is designated SEQ ID:3121, and is provided hereinbelow with reference to the sequence

listing part.

[19753] VGAM410 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM410 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM410 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19754] VGAM410 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM410 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM410 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM410 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM410 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19755] The complementary binding of VGAM410 RNA, herein designated VGAM RNA, to host target binding sites on VGAM410 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM410 host target RNA into VGAM410 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19756] It is appreciated that VGAM410 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM410 host target genes. The mRNA of each one of this plurality of VGAM410 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM410 RNA, herein designated VGAM



RNA, and which when bound by VGAM410 RNA causes inhibition of translation of respective one or more VGAM410 host target proteins.

[19757] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM410 gene, herein designated VGAM GENE, on one or more VGAM410 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19758] It is yet further appreciated that a function of VGAM410 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM410 include diagnosis, prevention and treatment of viral infection by O'nyong-nyong Virus. Specific functions, and accordingly utilities, of VGAM410 correlate with, and may be deduced from, the identity of the host target genes which VGAM410 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [19759] Nucleotide sequences of the VGAM410 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM410 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM410 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM410 are further described hereinbelow with reference to Table 1.
- [19760] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM410 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM410 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [19761] As mentioned hereinabove with reference to Fig. 1, a function of VGAM410 gene, herein designated VGAM is

inhibition of expression of VGAM410 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM410 correlate with, and may be deduced from, the identity of the target genes which VGAM410 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19762] Carbohydrate (keratan sulfate Gal-6) Sulfotransferase 1 (CHST1, Accession NM\_003654) is a VGAM410 host target gene. CHST1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CHST1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST1 BINDING SITE, designated SEQ ID:9729, to the nucleotide sequence of VGAM410 RNA, herein designated VGAM RNA, also designated SEQ ID:3121.

[19763] A function of VGAM410 is therefore inhibition of Carbohydrate (keratan sulfate Gal-6) Sulfotransferase 1 (CHST1, Accession NM\_003654), a gene which may play a role in keratan sulfate biosynthesis in brain and cornea. Accordingly, utilities of VGAM410 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with CHST1. The function of CHST1 has been established by previous studies. The keratan sulfate proteoglycans lumican and keratocan are the major proteoglycans in the cornea and are thought to play an important role in corneal transparency. Sulfation appears to be important for the biologic function of keratan sulfate, because undersulfated keratan sulfate is synthesized in patients with macular corneal dystrophy (see OMIM Ref. No. 217800). Keratan sulfate bears sulfate groups on both N-acetylglucosamine (OMIM Ref. No. GlcNAc) and galactose residues. Fukuta et al. (1997) stated that C6ST (chondroitin 6-sulfotransferase; 603799) catalyzes sulfation of chondroitin and keratan sulfate. However, in developing cornea, keratan sulfate is actively synthesized while chondroitin 6-sulfate synthesis is minimal, suggesting that a different sulfotransferase is present in cornea with specificity towards keratan sulfate. By screening a human fetal brain library with a chick C6ST cDNA, Fukuta et al. (1997) isolated cDNAs encoding C6ST and keratan sulfate gal-6-sulfotransferase (KSGal6ST). Northern blot analysis revealed that the 2.8-kb KSGal6ST mRNA was expressed in human brain and in chick brain and cornea. A slightly larger and less abundant transcript was observed

in human skeletal muscle. The predicted 411-amino acid KSGal6ST shares 37% sequence identity with chick C6ST. When the KSGal6ST cDNA was expressed in COS-7 cells, keratan sulfate sulfotransferase activity increased, but C6ST activity did not. In vitro, the partially purified KS-Gal6ST protein showed substrate specificity towards keratan sulfate; KSGal6ST could not utilize chondroitin as an acceptor. Fukuta et al. (1997) concluded that KSGal6ST may participate in the biosynthesis of keratan sulfate in the brain and cornea. Independently, Mazany et al. (1998) cloned genomic DNA and cDNAs corresponding to CHST1, which they called C6ST. These authors found that stable expression of the CHST1 cDNA in CHO cells increased both C6ST and keratan sulfate sulfotransferase activities. Mazany et al. (1998) suggested that the distinct pattern of CHST1 enzyme activity observed by Fukuta et al. (1997) may be due to differences between the mammalian cell lines used by the 2 groups to express the enzyme.

[19764] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19765] Iida, A.; Saito, S.; Sekine, A.; Mishima, C.; Kitamura, Y.; Kondo, K.; Harigae, S.; Osawa, S.; Nakamura, Y. : Catalog

of 77 single-nucleotide polymorphisms (SNPs) in the carbohydrate sulfotransferase 1 (CHST1) and carbohydrate sulfotransferase 3 (CHST3) genes. J. Hum. Genet. 47: 14–19, 2002. ; and

[19766] Mazany, K. D.; Peng, T.; Watson, C. E.; Tabas, I.; Williams, K. J. : Human chondroitin 6-sulfotransferase: cloning, gene structure, and chromosomal localization. Biochim. Biophys. Acta.

[19767] Further studies establishing the function and utilities of CHST1 are found in John Hopkins OMIM database record ID 603797, and in cited publications numbered 994–996 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ11539 (Accession NM\_024748) is another VGAM410 host target gene. FLJ11539 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11539, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11539 BINDING SITE, designated SEQ ID:24084, to the nucleotide sequence of VGAM410 RNA, herein designated VGAM RNA, also designated SEQ ID:3121.

[19768] Another function of VGAM410 is therefore inhibition of FLJ11539 (Accession NM\_024748). Accordingly, utilities of VGAM410 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11539. FLJ23511 (Accession NM\_032239) is another VGAM410 host target gene. FLJ23511 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23511, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23511 BINDING SITE, designated SEQ ID:25964, to the nucleotide sequence of VGAM410 RNA, herein designated VGAM RNA, also designated SEQ ID:3121.

[19769] Another function of VGAM410 is therefore inhibition of FLJ23511 (Accession NM\_032239). Accordingly, utilities of VGAM410 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23511. PRO1866 (Accession NM\_018510) is another VGAM410 host target gene. PRO1866 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO1866, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1866 BINDING SITE, designated SEQ ID:20578, to the nucleotide sequence of VGAM410 RNA, herein designated VGAM RNA, also designated SEQ ID:3121.

[19770] Another function of VGAM410 is therefore inhibition of PRO1866 (Accession NM\_018510). Accordingly, utilities of VGAM410 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1866. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 411 (VGAM411) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19771] VGAM411 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM411 was detected is described hereinabove with reference to Figs. 1–8.

[19772] VGAM411 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Igbo Ora Virus. VGAM411 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the



human genome.

[19773] VGAM411 gene encodes a VGAM411 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM411 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM411 precursor RNA is designated SEQ ID:397, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:397 is located at position 3184 relative to the genome of Igbo Ora Virus.

[19774] VGAM411 precursor RNA folds onto itself, forming VGAM411 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19775] An enzyme complex designated DICER COMPLEX, `dices` the VGAM411 folded precursor RNA into VGAM411 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM411 RNA is designated SEQ ID:3122, and is provided hereinbelow with reference to the sequence listing part.

[19776] VGAM411 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM411 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM411 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19777] VGAM411 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM411 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM411 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM411 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM411 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19778] The complementary binding of VGAM411 RNA, herein designated VGAM RNA, to host target binding sites on VGAM411 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM411 host target RNA into VGAM411 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19779] It is appreciated that VGAM411 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM411 host target genes. The mRNA of each one of this plurality of VGAM411 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM411 RNA, herein designated VGAM RNA, and which when bound by VGAM411 RNA causes inhibition of translation of respective one or more VGAM411 host target proteins.

[19780] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM411 gene, herein designated VGAM GENE, on one or more VGAM411 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19781] It is yet further appreciated that a function of VGAM411 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM411 include diagnosis, prevention and treatment of viral infection by Igbo Ora Virus. Specific functions, and accordingly utilities, of VGAM411 correlate with, and may be deduced from, the identity of the host target genes which VGAM411 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19782] Nucleotide sequences of the VGAM411 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM411 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM411 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM411 are further described hereinbelow with reference to Table 1.

[19783] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM411 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM411 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19784] As mentioned hereinabove with reference to Fig. 1, a function of VGAM411 gene, herein designated VGAM is inhibition of expression of VGAM411 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM411 correlate with, and may be deduced from, the identity of the target genes which VGAM411 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19785] Nuclear Mitotic Apparatus Protein 1 (NUMA1, Accession XM\_167853) is a VGAM411 host target gene. NUMA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUMA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUMA1 BINDING SITE, designated SEQ ID:44881, to the nucleotide sequence of VGAM411 RNA, herein designated VGAM RNA, also designated SEQ ID:3122.

[19786] A function of VGAM411 is therefore inhibition of Nuclear Mitotic Apparatus Protein 1 (NUMA1, Accession XM\_167853), a gene which is nuclear mitotic apparatus protein. Accordingly, utilities of VGAM411 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUMA1. The function of NUMA1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM192.FLJ14642 (Accession NM\_032818) is another VGAM411 host target gene. FLJ14642 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14642, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14642 BINDING SITE, designated SEQ ID:26595, to the nucleotide sequence of VGAM411 RNA, herein designated VGAM RNA, also designated SEQ ID:3122.

[19787] Another function of VGAM411 is therefore inhibition of FLJ14642 (Accession NM\_032818). Accordingly, utilities of VGAM411 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14642.

KIAA1084 (Accession NM\_014910) is another VGAM411 host target gene. KIAA1084 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1084, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1084 BINDING SITE, designated SEQ ID:17139, to the nucleotide sequence of VGAM411 RNA, herein designated VGAM RNA, also designated SEQ ID:3122.

[19788] Another function of VGAM411 is therefore inhibition of KIAA1084 (Accession NM\_014910). Accordingly, utilities of VGAM411 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1084. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 412 (VGAM412) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19789] VGAM412 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The



method by which VGAM412 was detected is described hereinabove with reference to Figs. 1–8.

[19790] VGAM412 gene, herein designated VGAM GENE, is a viral gene contained in the genome of O'nyong–nyong Virus.

VGAM412 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19791] VGAM412 gene encodes a VGAM412 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM412 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM412 precursor RNA is designated SEQ ID:398, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:398 is located at position 4500 relative to the genome of O'nyong–nyong Virus.

[19792] VGAM412 precursor RNA folds onto itself, forming VGAM412 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two–dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19793] An enzyme complex designated DICER COMPLEX, `dices` the VGAM412 folded precursor RNA into VGAM412 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 67%) nucleotide sequence of VGAM412 RNA is designated SEQ ID:3123, and is provided hereinbelow with reference to the sequence listing part.

[19794] VGAM412 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM412 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM412 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19795] VGAM412 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM412 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM412 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM412 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM412 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[19796] The complementary binding of VGAM412 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM412 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM412 host target RNA into VGAM412 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19797] It is appreciated that VGAM412 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM412 host target genes. The mRNA of each one of this plurality of VGAM412 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM412 RNA, herein designated VGAM RNA, and which when bound by VGAM412 RNA causes inhibition of translation of respective one or more VGAM412 host target proteins.

[19798] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM412 gene, herein designated VGAM GENE, on one or more VGAM412 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19799] It is yet further appreciated that a function of VGAM412 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of viral infection by O'nyong-nyong Virus. Specific functions, and accordingly utilities, of VGAM412 correlate with, and may be deduced from, the identity of the host target genes which VGAM412 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19800] Nucleotide sequences of the VGAM412 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM412 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM412 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM412 are further described hereinbelow with reference to Table 1.

[19801] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM412 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM412 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19802] As mentioned hereinabove with reference to Fig. 1, a function of VGAM412 gene, herein designated VGAM is inhibition of expression of VGAM412 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM412 correlate with, and may be deduced from, the identity of the target genes which VGAM412 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19803] Deafness, Autosomal Dominant 5 (DFNA5, Accession NM\_004403) is a VGAM412 host target gene. DFNA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DFNA5, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DFNA5 BINDING SITE, designated SEQ ID:10655, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19804] A function of VGAM412 is therefore inhibition of Deafness, Autosomal Dominant 5 (DFNA5, Accession NM\_004403). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DFNA5. ATPase, H<sup>+</sup> Transporting, Lysosomal 56/58kDa, V1 Subunit B, Isoform 2 (ATP6V1B2, Accession NM\_001693) is another VGAM412 host target gene. ATP6V1B2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP6V1B2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP6V1B2 BINDING SITE, designated SEQ ID:7413, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19805] Another function of VGAM412 is therefore inhibition of

ATPase, H<sup>+</sup> Transporting, Lysosomal 56/58kDa, V1 Sub-unit B, Isoform 2 (ATP6V1B2, Accession NM\_001693). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP6V1B2. FLJ11053 (Accession XM\_114194) is another VGAM412 host target gene. FLJ11053 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11053, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11053 BINDING SITE, designated SEQ ID:42778, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19806] Another function of VGAM412 is therefore inhibition of FLJ11053 (Accession XM\_114194). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11053. KIAA0478 (Accession NM\_014870) is another VGAM412 host target gene. KIAA0478 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0478, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0478 BINDING SITE, designated SEQ ID:16988, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19807] Another function of VGAM412 is therefore inhibition of KIAA0478 (Accession NM\_014870). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0478. KIAA1404 (Accession XM\_030494) is another VGAM412 host target gene. KIAA1404 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1404, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1404 BINDING SITE, designated SEQ ID:31052, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19808] Another function of VGAM412 is therefore inhibition of KIAA1404 (Accession XM\_030494). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1404. LanC Lantibiotic Synthetase Component C-like 2 (bacterial) (LANCL2, Accession NM\_018697) is another VGAM412 host target gene. LANCL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LANCL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LANCL2 BINDING SITE, designated SEQ ID:20780, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19809] Another function of VGAM412 is therefore inhibition of LanC Lantibiotic Synthetase Component C-like 2 (bacterial) (LANCL2, Accession NM\_018697). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LANCL2. OS-9 (Accession NM\_006812) is another VGAM412 host target gene. OS-9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OS-9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OS-9 BINDING SITE, designated SEQ ID:20781, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

tarity of the nucleotide sequences of OS-9 BINDING SITE, designated SEQ ID:13682, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19810] Another function of VGAM412 is therefore inhibition of OS-9 (Accession NM\_006812). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OS-9. PRO1483 (Accession NM\_018582) is another VGAM412 host target gene. PRO1483 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO1483, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1483 BINDING SITE, designated SEQ ID:20660, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19811] Another function of VGAM412 is therefore inhibition of PRO1483 (Accession NM\_018582). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1483. RASD Family, Member 2 (RASD2, Accession NM\_014310)

is another VGAM412 host target gene. RASD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RASD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASD2 BINDING SITE, designated SEQ ID:15604, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19812] Another function of VGAM412 is therefore inhibition of RASD Family, Member 2 (RASD2, Accession NM\_014310). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASD2. LOC132332 (Accession XM\_072306) is another VGAM412 host target gene. LOC132332 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC132332, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC132332 BINDING SITE, designated SEQ ID:37486, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3123.

[19813] Another function of VGAM412 is therefore inhibition of LOC132332 (Accession XM\_072306). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC132332. LOC92148 (Accession XM\_043160) is another VGAM412 host target gene. LOC92148 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92148, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92148 BINDING SITE, designated SEQ ID:33910, to the nucleotide sequence of VGAM412 RNA, herein designated VGAM RNA, also designated SEQ ID:3123.

[19814] Another function of VGAM412 is therefore inhibition of LOC92148 (Accession XM\_043160). Accordingly, utilities of VGAM412 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92148. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 413 (VGAM413) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19815] VGAM413 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM413 was detected is described hereinabove with reference to Figs. 1–8.

[19816] VGAM413 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pepper Mottle Virus. VGAM413 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19817] VGAM413 gene encodes a VGAM413 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM413 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM413 precursor RNA is designated SEQ ID:399, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:399 is located at position 7131 relative to the genome of Pepper Mottle Virus.

[19818] VGAM413 precursor RNA folds onto itself, forming

VGAM413 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19819] An enzyme complex designated DICER COMPLEX, `dices` the VGAM413 folded precursor RNA into VGAM413 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 70%) nucleotide sequence of VGAM413 RNA is designated SEQ ID:3124, and is provided hereinbelow with reference to the sequence listing part.

[19820] VGAM413 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM413 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM413 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19821] VGAM413 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM413 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM413 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM413 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM413 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example



only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19822] The complementary binding of VGAM413 RNA, herein designated VGAM RNA, to host target binding sites on VGAM413 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM413 host target RNA into VGAM413 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19823] It is appreciated that VGAM413 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM413 host target genes. The mRNA of each one of this plurality of VGAM413 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM413 RNA, herein designated VGAM RNA, and which when bound by VGAM413 RNA causes inhibition of translation of respective one or more VGAM413 host target proteins.

[19824] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM413 gene, herein designated VGAM GENE, on one or more VGAM413 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19825] It is yet further appreciated that a function of VGAM413 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of viral infection by Pepper Mottle Virus. Specific functions, and accordingly utilities, of VGAM413 correlate with, and may be deduced from, the identity of the host target genes which VGAM413 binds and inhibits, and

the function of these host target genes, as elaborated hereinbelow.

[19826] Nucleotide sequences of the VGAM413 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM413 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM413 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM413 are further described hereinbelow with reference to Table 1.

[19827] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM413 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM413 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19828] As mentioned hereinabove with reference to Fig. 1, a function of VGAM413 gene, herein designated VGAM is inhibition of expression of VGAM413 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM413 correlate with, and may be deduced from, the identity of the target genes which VGAM413 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[19829] Eukaryotic Translation Initiation Factor 2C, 1 (EIF2C1, Accession NM\_012199) is a VGAM413 host target gene. EIF2C1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF2C1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF2C1 BINDING SITE, designated SEQ ID:14502, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19830] A function of VGAM413 is therefore inhibition of Eukaryotic Translation Initiation Factor 2C, 1 (EIF2C1, Accession NM\_012199), a gene which plays an important role in the eukaryotic peptide chain initiation process. Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF2C1. The function of EIF2C1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM118.G Protein-coupled Receptor 81 (GPR81, Accession NM\_032554) is another VGAM413

host target gene. GPR81 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR81, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR81 BINDING SITE, designated SEQ ID:26282, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19831] Another function of VGAM413 is therefore inhibition of G Protein-coupled Receptor 81 (GPR81, Accession NM\_032554). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR81. Potassium Voltage-gated Channel, Shaker-related Subfamily, Member 5 (KCNA5, Accession XM\_006988) is another VGAM413 host target gene. KCNA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNA5 BINDING SITE, designated SEQ ID:30028, to the nucleotide sequence of VGAM413

RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19832] Another function of VGAM413 is therefore inhibition of Potassium Voltage-gated Channel, Shaker-related Subfamily, Member 5 (KCNA5, Accession XM\_006988), a gene which mediates the voltage-dependent potassium ion permeability of excitable membranes. Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNA5. The function of KCNA5 has been established by previous studies. Potassium channels play an important role in the regulation of pancreatic beta cells in response to glucose and the sulfonylurea oral hypoglycemic agents. Philipson et al. (1991) used a rat brain potassium channel probe to screen a human insulinoma cDNA library for clones encoding voltage-gated potassium channels. They isolated a series of cDNA clones which were then used to isolate and sequence a potassium channel gene, designated PCN1. Microinjection of synthetic RNA encoding PCN1 was accomplished in order to determine the electrophysiologic characteristics of the protein. These experiments demonstrated that the PCN1 potassium channel has the electrophysiologic characteristics of delayed-rec-

tifier type channels. Tamkun et al. (1991) isolated human heart cDNAs encoding PCN1, which they called HK2, and HK1 (KCNA4; 176266). They reported that the predicted 605-amino acid HK2 protein shares the characteristics of voltage-gated potassium channels, with 6 potential membrane-spanning domains and a positively charged region in the fourth membrane-spanning domain. Northern blot analysis revealed that HK2 is expressed as a major 2.5- and a minor 1.5-kb mRNA in human atrium and ventricle. By study of somatic cell hybrids, McPherson et al. (1991) mapped a Shaker-related potassium voltage-gated channel gene to chromosome 12. Designated here KCNA5, the gene was identified with probe Kv1 from the rat. By multipoint linkage analysis of 8 CEPH families, Phromchotikul et al. (1993) mapped the KCNA5 gene to 12p and determined its position relative to 4 DNA markers. Using interspecific backcrosses between *Mus musculus* and *Mus spretus*, Klocke et al. (1993) mapped the *Kcna5* gene to a cluster with the *Kcna1* and *Kcna6* (OMIM Ref. No. 176257) genes and the mouse homolog of TPI1 (OMIM Ref. No. 190450). Since TPI1 is located on band 12p13 in the human, the 3 K(+)-channel genes was predicted to be in the same band. Curran et al. (1992) mapped the KCNA5 gene,

which they erroneously referred to as the KCNA1 gene, to chromosome 12 by use of human–rodent somatic cell panels and narrowed the localization to the distal short arm by in situ hybridization. Linkage studies had shown a maximum lod score of 2.72 at a recombination fraction of 0.05 between KCNA5 and the von Willebrand locus (VWF; 193400). Albrecht et al. (1995) determined that a 300–kb cluster on chromosome 12p13 contains the human KCNA6, KCNA1, and KCNA5 genes arranged in tandem

[19833] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19834] Albrecht, B.; Weber, K.; Pongs, O. : Characterization of a voltage–activated K–channel gene cluster on human chromosome 12p13. *Receptors Channels* 3: 213–220, 1995. ; and

[19835] Curran, M. E.; Landes, G. M.; Keating, M. T. : Molecular cloning, characterization, and genomic localization of a human potassium channel gene. *Genomics* 12: 729–737, 1992.

[19836] Further studies establishing the function and utilities of KCNA5 are found in John Hopkins OMIM database record ID 176267, and in cited publications numbered 10288,



10291, 1092 and 10939 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Lipin 1 (LPIN1, Accession XM\_041136) is another VGAM413 host target gene. LPIN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LPIN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LPIN1 BINDING SITE, designated SEQ ID:33467, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19837] Another function of VGAM413 is therefore inhibition of Lipin 1 (LPIN1, Accession XM\_041136), a gene which is involved in adipocyte differentiation (by similarity). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LPIN1. The function of LPIN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM35. Pleiomorphic Adenoma Gene 1 (PLAG1, Accession NM\_002655) is another VGAM413 host target gene. PLAG1 BINDING SITE is HOST TARGET binding

site found in the 3` untranslated region of mRNA encoded by PLAG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLAG1 BINDING SITE, designated SEQ ID:8520, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19838] Another function of VGAM413 is therefore inhibition of Pleiomorphic Adenoma Gene 1 (PLAG1, Accession NM\_002655), a gene which contains a zinc finger domain. Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLAG1. The function of PLAG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM29. Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase Activation Protein, Gamma Polypeptide (YWHAG, Accession NM\_012479) is another VGAM413 host target gene. YWHAG BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by YWHAG, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of YWHAG BINDING SITE, designated SEQ ID:14855, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19839] Another function of VGAM413 is therefore inhibition of Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase Activation Protein, Gamma Polypeptide (YWHAG, Accession NM\_012479), a gene which mediates mitogenic signals of PDGF in vascular smooth muscle cells. Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with YWHAG. The function of YWHAG and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM180.Chromosome 1 Open Reading Frame 22 (C1orf22, Accession NM\_025191) is another VGAM413 host target gene. C1orf22 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1orf22, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1orf22 BINDING SITE, designated SEQ ID:24837, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19840] Another function of VGAM413 is therefore inhibition of Chromosome 1 Open Reading Frame 22 (C1orf22, Accession NM\_025191). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf22. FLJ10246 (Accession NM\_018038) is another VGAM413 host target gene. FLJ10246 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10246, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10246 BINDING SITE, designated SEQ ID:19785, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19841] Another function of VGAM413 is therefore inhibition of FLJ10246 (Accession NM\_018038). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ10246. FLJ10276 (Accession NM\_018045) is another VGAM413 host target gene. FLJ10276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10276 BINDING SITE, designated SEQ ID:19791, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19842] Another function of VGAM413 is therefore inhibition of FLJ10276 (Accession NM\_018045). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10276. FLJ12700 (Accession NM\_024910) is another VGAM413 host target gene. FLJ12700 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12700 BINDING SITE, designated SEQ ID:24415, to the nucleotide sequence of

VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19843] Another function of VGAM413 is therefore inhibition of FLJ12700 (Accession NM\_024910). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12700. G2 (Accession XM\_039515) is another VGAM413 host target gene. G2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by G2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of G2 BINDING SITE, designated SEQ ID:33112, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19844] Another function of VGAM413 is therefore inhibition of G2 (Accession XM\_039515). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with G2. KIAA1655 (Accession XM\_039442) is another VGAM413 host target gene. KIAA1655 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1655, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1655 BINDING SITE, designated SEQ ID:33087, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19845] Another function of VGAM413 is therefore inhibition of KIAA1655 (Accession XM\_039442). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1655. Molybdenum Cofactor Synthesis 3 (MOCS3, Accession NM\_014484) is another VGAM413 host target gene. MOCS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MOCS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MOCS3 BINDING SITE, designated SEQ ID:15829, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19846] Another function of VGAM413 is therefore inhibition of Molybdenum Cofactor Synthesis 3 (MOCS3, Accession

NM\_014484). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MOCS3. P66 (Accession NM\_020699) is another VGAM413 host target gene. P66 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P66, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P66 BINDING SITE, designated SEQ ID:21843, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19847] Another function of VGAM413 is therefore inhibition of P66 (Accession NM\_020699). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P66. PRO0529 (Accession NM\_014074) is another VGAM413 host target gene. PRO0529 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO0529, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0529 BINDING SITE,



designated SEQ ID:15301, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19848] Another function of VGAM413 is therefore inhibition of PRO0529 (Accession NM\_014074). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0529. RA-GEF-2 (Accession NM\_016340) is another VGAM413 host target gene. RA-GEF-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RA-GEF-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RA-GEF-2 BINDING SITE, designated SEQ ID:18465, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19849] Another function of VGAM413 is therefore inhibition of RA-GEF-2 (Accession NM\_016340). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RA-GEF-2. Zinc Finger Protein 17 (HPF3, KOX 10) (ZNF17, Accession XM\_091895) is another VGAM413 host target

gene. ZNF17 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZNF17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF17 BINDING SITE, designated SEQ ID:40067, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19850] Another function of VGAM413 is therefore inhibition of Zinc Finger Protein 17 (HPF3, KOX 10) (ZNF17, Accession XM\_091895). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF17. LOC128077 (Accession XM\_059208) is another VGAM413 host target gene. LOC128077 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC128077, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC128077 BINDING SITE, designated SEQ ID:36916, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3124.

[19851] Another function of VGAM413 is therefore inhibition of LOC128077 (Accession XM\_059208). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC128077. LOC149127 (Accession XM\_097584) is another VGAM413 host target gene. LOC149127 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149127, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149127 BINDING SITE, designated SEQ ID:40949, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19852] Another function of VGAM413 is therefore inhibition of LOC149127 (Accession XM\_097584). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149127. LOC150630 (Accession XM\_097931) is another VGAM413 host target gene. LOC150630 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150630, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150630 BINDING SITE, designated SEQ ID:41239, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19853] Another function of VGAM413 is therefore inhibition of LOC150630 (Accession XM\_097931). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150630. LOC169021 (Accession XM\_095459) is another VGAM413 host target gene. LOC169021 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC169021, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169021 BINDING SITE, designated SEQ ID:40258, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19854] Another function of VGAM413 is therefore inhibition of LOC169021 (Accession XM\_095459). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC169021. LOC221687 (Accession XM\_166423) is another VGAM413 host target gene. LOC221687 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221687 BINDING SITE, designated SEQ ID:44306, to the nucleotide sequence of VGAM413 RNA, herein designated VGAM RNA, also designated SEQ ID:3124.

[19855] Another function of VGAM413 is therefore inhibition of LOC221687 (Accession XM\_166423). Accordingly, utilities of VGAM413 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221687. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 414 (VGAM414) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19856] VGAM414 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM414 was detected is described hereinabove with reference to Figs. 1–8.

[19857] VGAM414 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pepper Mottle Virus. VGAM414 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19858] VGAM414 gene encodes a VGAM414 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM414 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM414 precursor RNA is designated SEQ ID:400, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:400 is located at position 8752 relative to the genome of Pepper Mottle Virus.

[19859] VGAM414 precursor RNA folds onto itself, forming VGAM414 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19860] An enzyme complex designated DICER COMPLEX, `dices` the VGAM414 folded precursor RNA into VGAM414 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM414 RNA is designated SEQ ID:3125, and is provided hereinbelow with reference to the sequence listing part.

[19861] VGAM414 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM414 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM414 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19862] VGAM414 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM414 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM414 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM414 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM414 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19863] The complementary binding of VGAM414 RNA, herein



designated VGAM RNA, to host target binding sites on VGAM414 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM414 host target RNA into VGAM414 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19864] It is appreciated that VGAM414 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM414 host target genes. The mRNA of each one of this plurality of VGAM414 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM414 RNA, herein designated VGAM RNA, and which when bound by VGAM414 RNA causes inhibition of translation of respective one or more VGAM414 host target proteins.

[19865] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM414 gene, herein designated VGAM GENE, on one or more VGAM414 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19866] It is yet further appreciated that a function of VGAM414 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of viral infection by Pepper Mottle Virus. Specific functions, and accordingly utilities, of VGAM414 correlate with, and may be deduced from, the identity of the host target genes which VGAM414 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19867] Nucleotide sequences of the VGAM414 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM414 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM414 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM414 are further described hereinbelow with reference to Table 1.

[19868] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM414 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM414 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19869] As mentioned hereinabove with reference to Fig. 1, a function of VGAM414 gene, herein designated VGAM is inhibition of expression of VGAM414 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM414 correlate with, and may be deduced from, the identity of the target genes which VGAM414 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19870] Aldehyde Dehydrogenase 1 Family, Member B1 (ALDH1B1, Accession NM\_000692) is a VGAM414 host target gene. ALDH1B1 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by ALDH1B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALDH1B1 BINDING SITE, designated SEQ ID:6346, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19871] A function of VGAM414 is therefore inhibition of Aldehyde Dehydrogenase 1 Family, Member B1 (ALDH1B1, Accession NM\_000692). Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALDH1B1. Cytochrome P450, Subfamily VIIA (cholesterol 7 alpha-monooxygenase), Polypeptide 1 (CYP7A1, Accession NM\_000780) is another VGAM414 host target gene. CYP7A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP7A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP7A1 BINDING SITE, designated SEQ ID:6421, to the nucleotide sequence of VGAM414 RNA,

herein designated VGAM RNA, also designated SEQ ID:3125.

[19872] Another function of VGAM414 is therefore inhibition of Cytochrome P450, Subfamily VIIA (cholesterol 7 alpha-monooxygenase), Polypeptide 1 (CYP7A1, Accession NM\_000780), a gene which functions in cholesterol and bile acid metabolism . Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP7A1. The function of CYP7A1 has been established by previous studies. In an elegant series of experiments designed to understand the effect of retinoid X receptor (RXR; OMIM Ref. No. 180245) activation on cholesterol balance, Repa et al. (2000) treated animals with the rexinoid LG268. Animals treated with rexinoid exhibited marked changes in cholesterol balance, including inhibition of cholesterol absorption and repressed bile acid synthesis. Studies with receptor-selective agonists revealed that oxysterol receptors (LXRs, OMIM Ref. No. 602423 and 600380) and the bile acid receptor, FXR (OMIM Ref. No. 603826), are the RXR heterodimeric partners that mediate these effects by regulating expression of the reverse-cholesterol transporter, ABC1 (OMIM Ref. No. 600046), and the rate-

limiting enzyme of bile acid synthesis, CYP7A1, respectively. These RXR heterodimers serve as key regulators in cholesterol homeostasis by governing reverse cholesterol transport from peripheral tissues, bile acid synthesis in liver, and cholesterol absorption in intestine. Activation of RXR/LXR heterodimers inhibits cholesterol absorption by upregulation of ABC1 expression in the small intestine. Activation of RXR/FXR heterodimers represses CYP7A1 expression and bile acid production, leading to a failure to solubilize and absorb cholesterol. Studies have shown that RXR/FXR-mediated repression of CYP7A1 is dominant over RXR/LXR-mediated induction of CYP7A1, which explains why the rexinoid represses rather than activates CYP7A1 (Lu et al., 2000). Activation of the LXR signaling pathway results in the upregulation of ABC1 in peripheral cells, including macrophages, to efflux free cholesterol for transport back to the liver through high density lipoprotein, where it is converted to bile acids by the LXR-mediated increase in CYP7A1 expression. Secretion of biliary cholesterol in the presence of increased bile acid pools normally results in enhanced reabsorption of cholesterol; however, with the increased expression of ABC1 and efflux of cholesterol back into the lumen, there

is a reduction in cholesterol absorption and net excretion of cholesterol and bile acid. Rexinoids therefore offer a novel class of agents for treating elevated cholesterol. Agellon et al. (2002) found that wildtype mice and mice transgenic for human CYP7A1 respond differently to cholesterol feeding. Cholesterol feeding stimulated Cyp7a1 mRNA abundance and enzymatic activity in wild-type mice, but repressed human CYP7A1 mRNA and activity in transgenic mice. In transfected hepatoma cells, cholesterol increased mouse Cyp7a1 gene promoter activity, but had no effect on the human CYP7A1 gene promoter. By electrophoretic mobility shift assays, Agellon et al. (2002) found interaction of LXR:RXR with the mouse promoter, but no binding to the human promoter.

[19873] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19874] Lu, T. T.; Makishima, M.; Repa, J. J.; Schoonjans, K.; Kerr, T. A.; Auwerx, J.; Mangelsdorf, D. J. : Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. *Molec. Cell* 6: 507–515, 2000. ; and

[19875] Agellon, L. B.; Drover, V. A. B.; Cheema, S. K.; Gbaguidi, G. F.; Walsh, A. : Dietary cholesterol fails to stimulate the hu–

man cholesterol 7- $\alpha$ -hydroxylase gene (CYP7A1) in transgeni.

[19876] Further studies establishing the function and utilities of CYP7A1 are found in John Hopkins OMIM database record ID 118455, and in cited publications numbered 12131-12136, 5941, 12137-12140, 594 and 12141 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Engrailed Homolog 2 (EN2, Accession NM\_001427) is another VGAM414 host target gene. EN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EN2 BINDING SITE, designated SEQ ID:7147, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19877] Another function of VGAM414 is therefore inhibition of Engrailed Homolog 2 (EN2, Accession NM\_001427), a gene which may be required for normal cerebellar development; a homeobox protein, very strongly similar to murine En2. Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical



conditions associated with EN2. The function of EN2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM232. Glutamate Dehydrogenase 1 (GLUD1, Accession NM\_005271) is another VGAM414 host target gene. GLUD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLUD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLUD1 BINDING SITE, designated SEQ ID:11775, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19878] Another function of VGAM414 is therefore inhibition of Glutamate Dehydrogenase 1 (GLUD1, Accession NM\_005271). Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLUD1. Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540) is another VGAM414 host target gene. ODF2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region

of mRNA encoded by ODF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ODF2 BINDING SITE, designated SEQ ID:8388, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19879] Another function of VGAM414 is therefore inhibition of Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540), a gene which is very strongly similar to rat Odf2 . Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ODF2. The function of ODF2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM363.Single-minded Homolog 2 (Drosophila) (SIM2, Accession NM\_009586) is another VGAM414 host target gene. SIM2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of SIM2 BINDING SITE, designated SEQ ID:14314, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19880] Another function of VGAM414 is therefore inhibition of Single-minded Homolog 2 (Drosophila) (SIM2, Accession NM\_009586), a gene which may be a master gene of cns development. Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIM2. The function of SIM2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM369. Zinc Finger Protein 278 (ZNF278, Accession NM\_032050) is another VGAM414 host target gene. ZNF278 BINDING SITE1 through ZNF278 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ZNF278, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF278 BINDING SITE1 through ZNF278 BINDING SITE3, designated SEQ ID:25771, SEQ ID:25780 and SEQ ID:15622 respectively, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA,

also designated SEQ ID:3125.

[19881] Another function of VGAM414 is therefore inhibition of Zinc Finger Protein 278 (ZNF278, Accession NM\_032050), a gene which represses basal transcription as well as RNF4-mediated activation. Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF278. The function of ZNF278 has been established by previous studies. By chromatographic and coimmunoprecipitation analyses, Fedele et al. (2000) showed that ZNF278 interacts with RNF4 both in vitro and in vivo. The authors found that the POZ domain is responsible for repression of basal transcription as well as repression of RNF4-mediated activation. Immunofluorescence analysis demonstrated that ZNF278 colocalizes with RNF4 in the nuclear matrix

[19882] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19883] Fedele, M.; Benvenuto, G.; Pero, R.; Majello, B.; Battista, S.; Lembo, F.; Vollono, E.; Day, P. M.; Santoro, M.; Lania, L.; Bruni, C. B.; Fusco, A.; Chiariotti, L. : A novel member of the BTB/POZ family, PATZ, associates with the RNF4 RING

finger protein and acts as a transcriptional repressor. J. Biol. Chem. 275: 7894–7901, 2000. ; and

[19884] Mastrangelo, T.; Modena, P.; Tornielli, S.; Bullrich, F.; Testi, M. A.; Mezzelani, A.; Radice, P.; Azzarelli, A.; Pilotti, S.; Croce, C. M.; Pierotti, M. A.; Sozzi, G. : A novel zinc finge.

[19885] Further studies establishing the function and utilities of ZNF278 are found in John Hopkins OMIM database record ID 605165, and in sited publications numbered 4395–439 and 3660 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ20373 (Accession NM\_017792) is another VGAM414 host target gene. FLJ20373 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20373, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20373 BINDING SITE, designated SEQ ID:19426, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19886] Another function of VGAM414 is therefore inhibition of FLJ20373 (Accession NM\_017792). Accordingly, utilities of

VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20373. Serine Palmitoyltransferase, Long Chain Base Subunit 2 (SPTLC2, Accession NM\_004863) is another VGAM414 host target gene. SPTLC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPTLC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPTLC2 BINDING SITE, designated SEQ ID:11274, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19887] Another function of VGAM414 is therefore inhibition of Serine Palmitoyltransferase, Long Chain Base Subunit 2 (SPTLC2, Accession NM\_004863). Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPTLC2. LOC91170 (Accession XM\_036612) is another VGAM414 host target gene. LOC91170 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91170 BINDING SITE, designated SEQ ID:32481, to the nucleotide sequence of VGAM414 RNA, herein designated VGAM RNA, also designated SEQ ID:3125.

[19888] Another function of VGAM414 is therefore inhibition of LOC91170 (Accession XM\_036612). Accordingly, utilities of VGAM414 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91170. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 415 (VGAM415) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19889] VGAM415 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM415 was detected is described hereinabove with reference to Figs. 1–8.

[19890] VGAM415 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pepper Mottle Virus. VGAM415 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[19891] VGAM415 gene encodes a VGAM415 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM415 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM415 precursor RNA is designated SEQ ID:401, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:401 is located at position 792 relative to the genome of Pepper Mottle Virus.

[19892] VGAM415 precursor RNA folds onto itself, forming VGAM415 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19893] An enzyme complex designated DICER COMPLEX, `dices` the VGAM415 folded precursor RNA into VGAM415 RNA,



herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM415 RNA is designated SEQ ID:3126, and is provided hereinbelow with reference to the sequence listing part.

[19894] VGAM415 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM415 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM415 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19895] VGAM415 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM415 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM415 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM415 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM415 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19896] The complementary binding of VGAM415 RNA, herein designated VGAM RNA, to host target binding sites on VGAM415 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM415 host target RNA into VGAM415 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[19897] It is appreciated that VGAM415 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM415 host target genes. The mRNA of each one of this plurality of VGAM415 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM415 RNA, herein designated VGAM RNA, and which when bound by VGAM415 RNA causes inhibition of translation of respective one or more VGAM415 host target proteins.

[19898] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM415 gene, herein designated VGAM GENE, on one or more VGAM415 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19899] It is yet further appreciated that a function of VGAM415 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of viral infection by Pepper Mottle Virus. Specific functions, and accordingly utilities, of VGAM415 correlate with, and may be deduced from, the identity of the host target genes which VGAM415 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19900] Nucleotide sequences of the VGAM415 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM415 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM415 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM415 are further described hereinbelow with reference to Table 1.

[19901] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM415 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM415 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19902] As mentioned hereinabove with reference to Fig. 1, a function of VGAM415 gene, herein designated VGAM is inhibition of expression of VGAM415 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM415 correlate with, and may be deduced from, the identity of the target genes which VGAM415 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19903] EGF-like-domain, Multiple 4 (EGFL4, Accession XM\_029883) is a VGAM415 host target gene. EGFL4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGFL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGFL4 BINDING SITE, designated SEQ ID:30962, to the nucleotide sequence of VGAM415 RNA, herein designated

VGAM RNA, also designated SEQ ID:3126.

[19904] A function of VGAM415 is therefore inhibition of EGF-like-domain, Multiple 4 (EGFL4, Accession XM\_029883). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGFL4. Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010) is another VGAM415 host target gene. NRCAM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRCAM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRCAM BINDING SITE, designated SEQ ID:11446, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19905] Another function of VGAM415 is therefore inhibition of Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010), a gene which functions as a cell surface protein and belongs to the immunoglobulin superfamily. Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRCAM. The function of NRCAM and its

association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM268.ARPP-21 (Accession NM\_016300) is another VGAM415 host target gene. ARPP-21 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARPP-21, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARPP-21 BINDING SITE, designated SEQ ID:18419, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19906] Another function of VGAM415 is therefore inhibition of ARPP-21 (Accession NM\_016300). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARPP-21. UDP-GlcNAc:betaGal Beta-1,3-N-acetylglucosaminyltransferase 7 (B3GNT7, Accession XM\_048735) is another VGAM415 host target gene. B3GNT7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by B3GNT7, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B3GNT7 BINDING SITE, designated SEQ ID:35237, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19907] Another function of VGAM415 is therefore inhibition of UDP-GlcNAc:betaGal Beta-1,3-N-acetylglucosaminyltransferase 7 (B3GNT7, Accession XM\_048735). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B3GNT7. FLJ11722 (Accession NM\_024970) is another VGAM415 host target gene. FLJ11722 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11722, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11722 BINDING SITE, designated SEQ ID:24519, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19908] Another function of VGAM415 is therefore inhibition of



FLJ11722 (Accession NM\_024970). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11722. FLJ20006 (Accession NM\_017618) is another VGAM415 host target gene. FLJ20006 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20006, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20006 BINDING SITE, designated SEQ ID:19118, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19909] Another function of VGAM415 is therefore inhibition of FLJ20006 (Accession NM\_017618). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20006. FLJ20958 (Accession NM\_022102) is another VGAM415 host target gene. FLJ20958 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20958, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ20958 BINDING SITE, designated SEQ ID:22645, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19910] Another function of VGAM415 is therefore inhibition of FLJ20958 (Accession NM\_022102). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20958. GLTP (Accession NM\_016433) is another VGAM415 host target gene. GLTP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLTP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLTP BINDING SITE, designated SEQ ID:18554, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19911] Another function of VGAM415 is therefore inhibition of GLTP (Accession NM\_016433). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLTP. KIAA1001 (Accession NM\_014960) is another VGAM415

host target gene. KIAA1001 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1001, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1001 BINDING SITE, designated SEQ ID:17323, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19912] Another function of VGAM415 is therefore inhibition of KIAA1001 (Accession NM\_014960). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1001. KIAA1160 (Accession NM\_020701) is another VGAM415 host target gene. KIAA1160 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1160, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1160 BINDING SITE, designated SEQ ID:21850, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19913] Another function of VGAM415 is therefore inhibition of KIAA1160 (Accession NM\_020701). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1160. KIAA1430 (Accession XM\_087593) is another VGAM415 host target gene. KIAA1430 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1430, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1430 BINDING SITE, designated SEQ ID:39356, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19914] Another function of VGAM415 is therefore inhibition of KIAA1430 (Accession XM\_087593). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1430. LRP15 (Accession NM\_052953) is another VGAM415 host target gene. LRP15 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LRP15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRP15 BINDING SITE, designated SEQ ID:27509, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19915] Another function of VGAM415 is therefore inhibition of LRP15 (Accession NM\_052953). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRP15. PTD002 (Accession NM\_016144) is another VGAM415 host target gene. PTD002 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTD002, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTD002 BINDING SITE, designated SEQ ID:18227, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19916] Another function of VGAM415 is therefore inhibition of PTD002 (Accession NM\_016144). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTD002.

LOC120400 (Accession XM\_061971) is another VGAM415 host target gene. LOC120400 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC120400, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120400 BINDING SITE, designated SEQ ID:37219, to the nucleotide sequence of VGAM415 RNA, herein designated VGAM RNA, also designated SEQ ID:3126.

[19917] Another function of VGAM415 is therefore inhibition of LOC120400 (Accession XM\_061971). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120400. LOC221399 (Accession XM\_168134) is another VGAM415 host target gene. LOC221399 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221399, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221399 BINDING SITE, designated SEQ ID:45047, to the nucleotide sequence of VGAM415 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3126.

[19918] Another function of VGAM415 is therefore inhibition of LOC221399 (Accession XM\_168134). Accordingly, utilities of VGAM415 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221399. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 416 (VGAM416) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19919] VGAM416 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM416 was detected is described hereinabove with reference to Figs. 1–8.

[19920] VGAM416 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pepper Mottle Virus. VGAM416 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19921] VGAM416 gene encodes a VGAM416 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM416 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM416 precursor RNA is designated SEQ ID:402, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:402 is located at position 7262 relative to the genome of Pepper Mottle Virus.

[19922] VGAM416 precursor RNA folds onto itself, forming VGAM416 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19923] An enzyme complex designated DICER COMPLEX, `dices` the VGAM416 folded precursor RNA into VGAM416 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex



comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM416 RNA is designated SEQ ID:3127, and is provided hereinbelow with reference to the sequence listing part.

[19924] VGAM416 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM416 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM416 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19925] VGAM416 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM416 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM416 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM416 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM416 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[19926] The complementary binding of VGAM416 RNA, herein designated VGAM RNA, to host target binding sites on VGAM416 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM416 host target RNA into VGAM416 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19927] It is appreciated that VGAM416 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM416 host target genes. The mRNA of

each one of this plurality of VGAM416 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM416 RNA, herein designated VGAM RNA, and which when bound by VGAM416 RNA causes inhibition of translation of respective one or more VGAM416 host target proteins.

[19928] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM416 gene, herein designated VGAM GENE, on one or more VGAM416 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[19929] It is yet further appreciated that a function of VGAM416 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM416 include diagnosis, prevention and treatment of viral infection by Pepper Mottle Virus. Specific functions, and accordingly utilities, of VGAM416 correlate with, and may be deduced from, the identity of the host target genes which VGAM416 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19930] Nucleotide sequences of the VGAM416 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM416 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM416 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM416 are further described hereinbelow with reference to Table 1.

[19931] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM416 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM416 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[19932] As mentioned hereinabove with reference to Fig. 1, a function of VGAM416 gene, herein designated VGAM is inhibition of expression of VGAM416 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM416 correlate with, and may be deduced from, the identity of the target genes which VGAM416 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19933] Filamin B, Beta (actin binding protein 278) (FLNB, Accession XM\_030806) is a VGAM416 host target gene. FLNB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLNB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLNB BINDING SITE, designated SEQ ID:31139, to the nucleotide sequence of VGAM416 RNA, herein designated VGAM RNA, also designated SEQ ID:3127.

[19934] A function of VGAM416 is therefore inhibition of Filamin B, Beta (actin binding protein 278) (FLNB, Accession XM\_030806), a gene which Filamin B, beta; binds actin,

interacts with cytoplasmic domain of Ibalpha. Accordingly, utilities of VGAM416 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLNB. The function of FLNB has been established by previous studies. The platelet Gplb complex (see OMIM Ref. No. 138720) mediates the adherence of platelets at the site of vascular injury through the binding of Gplb-alpha (OMIM Ref. No. 231200) to subendothelial von Willebrand factor (VWF; 193400). In platelets, the Gplb complex is tightly bound to the actin cytoskeleton via an interaction of Gplb-alpha with ABP280 (filamin A; 300017). Using a yeast 2-hybrid screen with the cytoplasmic tail of Gplb-alpha as bait, Takafuta et al. (1998) isolated partial cDNAs encoding a novel filamin homolog that they designated beta-filamin. They used the partial cDNAs to screen a placenta library and recovered additional cDNAs corresponding to the entire beta-filamin coding region. Like ABP280, the predicted 2,602-amino acid protein contains an N-terminal actin-binding domain, a backbone of 24 tandem repeats, and 2 hinge regions. Excluding the unique first hinge region of beta-filamin, the sequences of beta-filamin and ABP280 are 70% identical. Antibodies against beta-filamin detected a 280-kD pro-

tein on Western blots of human umbilical vein endothelial cell (HUVEC) extracts and stained normal human endothelial cells in culture and in situ. Using antigen-capture ELISA, Takafuta et al. (1998) found that beta-filamin associates with Gplb-alpha in both platelets and HUVEC extracts. They determined that the Gplb-alpha-binding domain in beta-filamin is in repeats 17-20, a region that corresponds to the Gplb-alpha-binding domain in ABP280. Northern blot analysis revealed that beta-filamin is expressed as 2 approximately 9.5-kb mRNAs in many adult tissues. The 2 different transcripts appear to result from use of alternative polyadenylation signals. Takafuta et al. (1998) concluded that beta-filamin is a new member of the filamin family that may have significance for Gplb-alpha function in endothelial cells and platelets. Independently, Xu et al. (1998) isolated cDNAs encoding beta-filamin, which they referred to as ABP278. These authors also identified alternatively spliced mRNAs encoding ABP276, a beta-filamin isoform missing the first hinge region. RT-PCR analysis indicated that the 2 isoforms were expressed at different relative levels in various human tissues. The addition of thyroid-stimulating hormone (TSH; OMIM Ref. No. 188530) to cultured thyroid follicular cells

induces rapid and profound disruption of actin microfilaments. Using serum from a Graves disease (OMIM Ref. No. 275000) patient, Leedman et al. (1993) identified a thyroid cDNA encoding TABP (truncated actin-binding protein), a predicted 195-amino acid protein with homology to the C terminus of ABP280. Both Xu et al. (1998) and Takafuta et al. (1998) considered TABP to be a truncated form of beta-filamin. Mutations in the presenilin genes PS1 (OMIM Ref. No. 104311) and PS2 (OMIM Ref. No. 600759) account for approximately 50% of early-onset familial Alzheimer disease (AD; 104300). Zhang et al. (1998) identified beta-filamin as filamin homolog 1 (FH1), a filamin-related protein that interacts with the loop regions of PS1 and PS2. A monoclonal antibody recognizing both ABP280 and FH1 bound to blood vessels and astrocytes in the normal brain. In the brains of AD patients, Zhang et al. (1998) observed staining also in neurofibrillary tangles, neuropil threads, and dystrophic neurites within some senile plaques. The authors stated that detection of these presenilin-interacting proteins in these brain structures suggests that ABP280 and FH1 may be involved in the development of AD and that interactions between presenilins and ABP280/FH1 may be functionally significant. Takafuta



et al. (1998) noted that the FH1 sequence is identical to the C-terminal 291 amino acids of beta-filamin except for 2 residues, making it very likely that FH1 represents the C-terminal region of beta-filamin. By analysis of somatic cell hybrids, Zhang et al. (1998) mapped the FH1 gene to chromosome 3. Takafuta et al. (1998) refined the map position to 3p21.1-p14.3 based on inclusion of a previously mapped STS within the beta-filamin sequence. By FISH, Brocker et al. (1999) assigned the FLNB gene to 3p14.3. Chakarova et al. (2000) mapped FLNB to 3p14 by radiation hybrid analysis.

[19935] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19936] Brocker, F.; Bardenheuer, W.; Vieten, L.; Julicher, K.; Werner, N.; Marquitan, G.; Michael, D.; Opalka, B.; Schutte, J. : Assignment of human filamin gene FLNB to human chromosome band 3p14.3 and identification of YACs containing the complete FLNB transcribed region. Cytogenet. Cell Genet. 85: 267-268, 1999. ; and

[19937] Chakarova, C.; Wehnert, M. S.; Uhl, K.; Sakthivel, S.; Vosberg, H.-P.; van der Ven, P. F. M.; Furst, D. O. : Genomic structure and fine mapping of the two human filamin gene

paralogues.

[19938] Further studies establishing the function and utilities of FLNB are found in John Hopkins OMIM database record ID 603381, and in cited publications numbered 7501, 750 and 5281–5282 listed in the bibliography section herein–below, which are also hereby incorporated by reference. LOC143310 (Accession XM\_084485) is another VGAM416 host target gene. LOC143310 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC143310, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143310 BINDING SITE, designated SEQ ID:37606, to the nucleotide sequence of VGAM416 RNA, herein designated VGAM RNA, also designated SEQ ID:3127.

[19939] Another function of VGAM416 is therefore inhibition of LOC143310 (Accession XM\_084485). Accordingly, utilities of VGAM416 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143310. LOC92719 (Accession XM\_046853) is another VGAM416 host target gene. LOC92719 BINDING SITE is HOST TARGET binding site found in the 3` un–

translated region of mRNA encoded by LOC92719, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92719 BINDING SITE, designated SEQ ID:34847, to the nucleotide sequence of VGAM416 RNA, herein designated VGAM RNA, also designated SEQ ID:3127.

[19940] Another function of VGAM416 is therefore inhibition of LOC92719 (Accession XM\_046853). Accordingly, utilities of VGAM416 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92719. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 417 (VGAM417) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19941] VGAM417 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM417 was detected is described hereinabove with reference to Figs. 1–8.

[19942] VGAM417 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Pepper Mottle Virus. VGAM417 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19943] VGAM417 gene encodes a VGAM417 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM417 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM417 precursor RNA is designated SEQ ID:403, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:403 is located at position 8444 relative to the genome of Pepper Mottle Virus.

[19944] VGAM417 precursor RNA folds onto itself, forming VGAM417 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19945] An enzyme complex designated DICER COMPLEX, `dices` the VGAM417 folded precursor RNA into VGAM417 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM417 RNA is designated SEQ ID:3128, and is provided hereinbelow with reference to the sequence listing part.

[19946] VGAM417 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM417 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM417 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19947] VGAM417 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM417 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM417 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM417 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM417 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19948] The complementary binding of VGAM417 RNA, herein designated VGAM RNA, to host target binding sites on VGAM417 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM417 host tar-

get RNA into VGAM417 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19949] It is appreciated that VGAM417 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM417 host target genes. The mRNA of each one of this plurality of VGAM417 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM417 RNA, herein designated VGAM RNA, and which when bound by VGAM417 RNA causes inhibition of translation of respective one or more VGAM417 host target proteins.

[19950] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM417 gene, herein designated VGAM GENE, on one or more VGAM417 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[19951] It is yet further appreciated that a function of VGAM417 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of viral infection by Pepper Mottle Virus. Specific functions, and accordingly utilities, of VGAM417 correlate with, and may be deduced from, the identity of the host target genes which VGAM417 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19952] Nucleotide sequences of the VGAM417 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM417 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM417 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM417 are further



described hereinbelow with reference to Table 1.

[19953] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM417 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM417 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19954] As mentioned hereinabove with reference to Fig. 1, a function of VGAM417 gene, herein designated VGAM is inhibition of expression of VGAM417 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM417 correlate with, and may be deduced from, the identity of the target genes which VGAM417 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19955] Calpain 10 (CAPN10, Accession NM\_023089) is a VGAM417 host target gene. CAPN10 BINDING SITE1 and CAPN10 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CAPN10, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of CAPN10 BINDING SITE1 and CAPN10 BINDING SITE2, designated SEQ ID:23358 and SEQ ID:23357 respectively, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19956] A function of VGAM417 is therefore inhibition of Calpain 10 (CAPN10, Accession NM\_023089), a gene which catalyzes limited proteolysis of substrates involved in cytoskeletal remodelling and signal transduction. Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAPN10. The function of CAPN10 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. RAB11A, Member RAS Oncogene Family (RAB11A, Accession NM\_004663) is another VGAM417 host target gene. RAB11A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB11A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB11A BINDING SITE, designated SEQ ID:11033, to the nucleotide

sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19957] Another function of VGAM417 is therefore inhibition of RAB11A, Member RAS Oncogene Family (RAB11A, Accession NM\_004663). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB11A. DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 28 (DDX28, Accession NM\_018380) is another VGAM417 host target gene. DDX28 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DDX28, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDX28 BINDING SITE, designated SEQ ID:20407, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19958] Another function of VGAM417 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 28 (DDX28, Accession NM\_018380). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDX28.

FLJ11608 (Accession NM\_024557) is another VGAM417 host target gene. FLJ11608 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11608, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11608 BINDING SITE, designated SEQ ID:23775, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19959] Another function of VGAM417 is therefore inhibition of FLJ11608 (Accession NM\_024557). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11608. HGC6.1.1 (Accession NM\_014354) is another VGAM417 host target gene. HGC6.1.1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HGC6.1.1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HGC6.1.1 BINDING SITE, designated SEQ ID:15683, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3128.

[19960] Another function of VGAM417 is therefore inhibition of HGC6.1.1 (Accession NM\_014354). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HGC6.1.1. KIAA0417 (Accession XM\_048898) is another VGAM417 host target gene. KIAA0417 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0417, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0417 BINDING SITE, designated SEQ ID:35293, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19961] Another function of VGAM417 is therefore inhibition of KIAA0417 (Accession XM\_048898). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0417. KIAA0766 (Accession NM\_014805) is another VGAM417 host target gene. KIAA0766 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0766, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0766 BINDING SITE, designated SEQ ID:16742, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19962] Another function of VGAM417 is therefore inhibition of KIAA0766 (Accession NM\_014805). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0766. LOC146733 (Accession XM\_097076) is another VGAM417 host target gene. LOC146733 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146733, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146733 BINDING SITE, designated SEQ ID:40726, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19963] Another function of VGAM417 is therefore inhibition of LOC146733 (Accession XM\_097076). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC146733. LOC254431 (Accession XM\_173024) is another VGAM417 host target gene. LOC254431 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC254431, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254431 BINDING SITE, designated SEQ ID:46289, to the nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19964] Another function of VGAM417 is therefore inhibition of LOC254431 (Accession XM\_173024). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254431. LOC92539 (Accession XM\_045632) is another VGAM417 host target gene. LOC92539 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC92539, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92539 BINDING SITE, designated SEQ ID:34498, to the

nucleotide sequence of VGAM417 RNA, herein designated VGAM RNA, also designated SEQ ID:3128.

[19965] Another function of VGAM417 is therefore inhibition of LOC92539 (Accession XM\_045632). Accordingly, utilities of VGAM417 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92539. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 418 (VGAM418) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19966] VGAM418 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM418 was detected is described hereinabove with reference to Figs. 1–8.

[19967] VGAM418 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pepper Mottle Virus. VGAM418 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19968] VGAM418 gene encodes a VGAM418 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM418 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM418 precursor RNA is designated SEQ ID:404, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:404 is located at position 4033 relative to the genome of Pepper Mottle Virus.

[19969] VGAM418 precursor RNA folds onto itself, forming VGAM418 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19970] An enzyme complex designated DICER COMPLEX, `dices` the VGAM418 folded precursor RNA into VGAM418 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM418 RNA is designated SEQ ID:3129, and is provided hereinbelow with reference to the sequence listing part.

[19971] VGAM418 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM418 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM418 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19972] VGAM418 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM418 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM418 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM418 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM418 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19973] The complementary binding of VGAM418 RNA, herein designated VGAM RNA, to host target binding sites on VGAM418 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM418 host target RNA into VGAM418 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19974] It is appreciated that VGAM418 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM418 host target genes. The mRNA of each one of this plurality of VGAM418 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM418 RNA, herein designated VGAM RNA, and which when bound by VGAM418 RNA causes inhibition of translation of respective one or more VGAM418 host target proteins.

[19975] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM418 gene, herein designated VGAM GENE, on one or more VGAM418 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[19976] It is yet further appreciated that a function of VGAM418 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM418 include diagnosis, prevention and treatment of viral infection by Pepper Mottle Virus. Specific functions, and accordingly utilities, of VGAM418 correlate with, and may be deduced from, the identity of the host target genes which VGAM418 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[19977] Nucleotide sequences of the VGAM418 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM418 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM418 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM418 are further described hereinbelow with reference to Table 1.

[19978] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM418 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM418 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[19979] As mentioned hereinabove with reference to Fig. 1, a function of VGAM418 gene, herein designated VGAM is inhibition of expression of VGAM418 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM418 correlate with, and may be deduced from, the identity of the target genes which VGAM418 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[19980] Lymphocyte Cytosolic Protein 1 (L-plastin) (LCP1, Accession NM\_002298) is a VGAM418 host target gene. LCP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LCP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LCP1 BINDING SITE, designated SEQ ID:8082, to the nucleotide sequence of VGAM418 RNA, herein designated VGAM RNA, also designated SEQ ID:3129.

[19981] A function of VGAM418 is therefore inhibition of Lymphocyte Cytosolic Protein 1 (L-plastin) (LCP1, Accession

NM\_002298), a gene which is involved in t cell antigen receptor mediated signaling. Accordingly, utilities of VGAM418 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LCP1. The function of LCP1 has been established by previous studies. Hamaguchi et al. (1982) described a genetic polymorphism of a major human lymphocyte cytosolic protein (LCP) of molecular weight 64,000, detected in PHA-stimulated peripheral blood lymphocytes by high-resolution 2-dimensional electrophoresis (O'Farrell, 1975; Klose, 1975). Three different phenotypes determined by 2 common alleles at a single locus were found. In Japanese, the frequency of the 2 alleles was 0.936 and 0.064, respectively. The polypeptide was not detected in HeLa cells, fibroblasts, red cells, serum, or cerebrum. Traces were found in liver, kidney and skeletal muscle. (Hamaguchi et al. (1982) demonstrated polymorphism in 3 others of about 100 polypeptides. The 4 were all cytosolic and since they were separated by isoelectric focusing, they are all charge variants. The molecular weights of the 3 other polymorphic lymphocyte cytosol polypeptides were 40, 49, and 100 kD; see 174880. This stands in contrast to the restricted genetic variability in fibroblast polypeptides

(Walton et al., 1979; McConkey et al., 1979; Giometti and Anderson, 1981).) Data on gene frequencies of allelic variants were tabulated by Roychoudhury and Nei (1988). Kondo et al. (1985) assigned the LCP1 gene to 13q14.1–q14.2 by the deletion/dosage method. They studied a patient with trisomy 13 who had 1.5 times the normal amount of protein, a patient with retinoblastoma and deletion of 13q12.3–q21.2 who had half the normal amount of protein, and a patient with retinoblastoma and deletion of 13q14.1–q31.2 who had lost the father's allele and had half the normal amount of protein (Kondo et al., 1985). Close linkage to ESD (OMIM Ref. No. 133280) was indicated by a maximum lod score of 4.221 at zero recombination. As part of an undertaking to map by genetic linkage human lymphocyte proteins that are genetically polymorphic in isoelectric point, Goldman et al. (1991) mapped the LCP1 gene to a site near the ESD locus on chromosome 13 by studies in 9 families from the CEPH collection. The proteins in the immortalized lymphocyte cell lines were analyzed by 2-dimensional electrophoresis. Murayama et al. (1993) demonstrated that L-plastin and LCP1 are identical and mapped the gene to 13q14.3. Lin et al. (1988) isolated partial cDNAs encoding L-plastin



and T-plastin (OMIM Ref. No. 300131) from a transformed human fibroblast cDNA library. Northern blot analysis revealed that L-plastin is expressed as a 3.7-kb mRNA in leukocytes, transformed fibroblasts, and a diverse array of human tumor cell lines. Zu et al. (1990) reported that L-plastin is identical to p65, an interleukin-2 (IL2; 147680)-stimulated phosphoprotein found in human T cells. Zu et al. (1990) isolated p65 cDNAs from a human T-lymphocyte cDNA library. The predicted 627-amino acid p65 protein contains 2 EF-hand calcium-binding domains, a calmodulin-binding site, and 2 tandem repeats of an actin-binding domain. Lin et al. (1993) reported that both the L-plastin and T-plastin genes contain 16 exons and span approximately 90 kb. Lin et al. (1997) found that the human and murine L-plastin promoters are highly homologous and function equally well in either human or murine leukocytes. The LAZ3 gene (BCL6; 109565) on 3q27 is nonrandomly disrupted in B-cell non-Hodgkin lymphoma by chromosomal translocations. Galiegue-Zouitina et al. (1999) identified the L-plastin gene as a novel LAZ3 partner in chimeric transcripts resulting from a t(3;13)(q27;q14) translocation in 2 cases of B-cell lymphoma. As a consequence of the translocation, the

5-prime regulatory region of each gene was exchanged, creating both LCP1-LAZ3 and reciprocal LAZ3-LCP1 fusion transcripts in one case, and only an LCP1-LAZ3 fusion transcript in the other.

[19982] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[19983] Galiegue-Zouitina, S.; Quief, S.; Hildebrand, M.-P.; Denis, C.; Detourmignies, L.; Lai, J.-L.; Kerckaert, J.-P. : Nonrandom fusion of L-plastin (LCP1) and LAZ3 (BCL6) genes by t(3;13)(q27;q14) chromosome translocation in two cases of B-cell non-Hodgkin lymphoma. *Genes Chromosomes Cancer* 26: 97-105, 1999. ; and

[19984] Lin, C.-S.; Park, T.; Chen, Z. P.; Leavitt, J. : Human plastin genes: comparative gene structure, chromosome location, and differential expression in normal and neoplastic cells. *J. Bi.*

[19985] Further studies establishing the function and utilities of LCP1 are found in John Hopkins OMIM database record ID 153430, and in cited publications numbered 607-608, 3850-616, 652-658, 1165 and 3780-662 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SON DNA Binding Protein (SON,

Accession NM\_058183) is another VGAM418 host target gene. SON BINDING SITE1 and SON BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SON, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SON BINDING SITE1 and SON BINDING SITE2, designated SEQ ID:27745 and SEQ ID:29041 respectively, to the nucleotide sequence of VGAM418 RNA, herein designated VGAM RNA, also designated SEQ ID:3129.

[19986] Another function of VGAM418 is therefore inhibition of SON DNA Binding Protein (SON, Accession NM\_058183). Accordingly, utilities of VGAM418 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SON. SH3 Domain Binding Glutamic Acid-rich Protein Like 2 (SH3BGRL2, Accession NM\_031469) is another VGAM418 host target gene. SH3BGRL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SH3BGRL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

SH3BGRL2 BINDING SITE, designated SEQ ID:25531, to the nucleotide sequence of VGAM418 RNA, herein designated VGAM RNA, also designated SEQ ID:3129.

[19987] Another function of VGAM418 is therefore inhibition of SH3 Domain Binding Glutamic Acid-rich Protein Like 2 (SH3BGRL2, Accession NM\_031469). Accordingly, utilities of VGAM418 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SH3BGRL2. LOC138389 (Accession XM\_072534) is another VGAM418 host target gene. LOC138389 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC138389, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC138389 BINDING SITE, designated SEQ ID:37504, to the nucleotide sequence of VGAM418 RNA, herein designated VGAM RNA, also designated SEQ ID:3129.

[19988] Another function of VGAM418 is therefore inhibition of LOC138389 (Accession XM\_072534). Accordingly, utilities of VGAM418 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC138389. LOC90246 (Accession XM\_030283) is an—

other VGAM418 host target gene. LOC90246 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90246, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90246 BINDING SITE, designated SEQ ID:30999, to the nucleotide sequence of VGAM418 RNA, herein designated VGAM RNA, also designated SEQ ID:3129.

[19989] Another function of VGAM418 is therefore inhibition of LOC90246 (Accession XM\_030283). Accordingly, utilities of VGAM418 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90246. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 419 (VGAM419) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[19990] VGAM419 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM419 was detected is described

hereinabove with reference to Figs. 1–8.

[19991] VGAM419 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pepper Mottle Virus.

VGAM419 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[19992] VGAM419 gene encodes a VGAM419 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM419 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM419 precursor RNA is designated SEQ ID:405, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:405 is located at position 6952 relative to the genome of Pepper Mottle Virus.

[19993] VGAM419 precursor RNA folds onto itself, forming VGAM419 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[19994] An enzyme complex designated DICER COMPLEX, `dices` the VGAM419 folded precursor RNA into VGAM419 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 54%) nucleotide sequence of VGAM419 RNA is designated SEQ ID:3130, and is provided hereinbelow with reference to the sequence listing part.

[19995] VGAM419 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM419 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM419 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[19996] VGAM419 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM419 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM419 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM419 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM419 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[19997] The complementary binding of VGAM419 RNA, herein designated VGAM RNA, to host target binding sites on VGAM419 host target RNA, herein designated VGAM HOST



TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM419 host target RNA into VGAM419 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[19998] It is appreciated that VGAM419 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM419 host target genes. The mRNA of each one of this plurality of VGAM419 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM419 RNA, herein designated VGAM RNA, and which when bound by VGAM419 RNA causes inhibition of translation of respective one or more VGAM419 host target proteins.

[19999] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM419 gene, herein designated VGAM GENE, on one or more VGAM419 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20000] It is yet further appreciated that a function of VGAM419 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of viral infection by Pepper Mottle Virus. Specific functions, and accordingly utilities, of VGAM419 correlate with, and may be deduced from, the identity of the host target genes which VGAM419 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20001] Nucleotide sequences of the VGAM419 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM419 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM419 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM419 are further described hereinbelow with reference to Table 1.

[20002] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM419 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM419 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20003] As mentioned hereinabove with reference to Fig. 1, a function of VGAM419 gene, herein designated VGAM is inhibition of expression of VGAM419 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM419 correlate with, and may be deduced from, the identity of the target genes which VGAM419 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20004] AXL Receptor Tyrosine Kinase (AXL, Accession NM\_021913) is a VGAM419 host target gene. AXL BINDING SITE1 and AXL BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by AXL, corresponding to HOST TARGET binding sites

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AXL BINDING SITE1 and AXL BINDING SITE2, designated SEQ ID:22442 and SEQ ID:7421 respectively, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20005] A function of VGAM419 is therefore inhibition of AXL Receptor Tyrosine Kinase (AXL, Accession NM\_021913). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AXL. Betaine-homocysteine Methyltransferase 2 (BHMT2, Accession NM\_017614) is another VGAM419 host target gene. BHMT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BHMT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BHMT2 BINDING SITE, designated SEQ ID:19117, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20006] Another function of VGAM419 is therefore inhibition of Betaine-homocysteine Methyltransferase 2 (BHMT2, Ac-

cession NM\_017614). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BHMT2. Carbohydrate Kinase-like (CARKL, Accession NM\_013276) is another VGAM419 host target gene. CARKL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CARKL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CARKL BINDING SITE, designated SEQ ID:14940, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20007] Another function of VGAM419 is therefore inhibition of Carbohydrate Kinase-like (CARKL, Accession NM\_013276), a gene which is a putative carbohydrate kinase and may be a modifier for the cystinosis phenotype. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CARKL. The function of CARKL has been established by previous studies. Touchman et al. (2000) sequenced 200 kb surrounding the gene encoding cystinosis (CTNS; 606272), which is mutated in nephropathic cystinosis

(OMIM Ref. No. 219800), on chromosome 17p13. They found that genomic sequence in this region matched known ESTs. Using PCR primers to amplify a human fetal kidney cDNA library, the authors cloned a cDNA, which they designated CARKL (carbohydrate kinase-like), encoding a deduced 478-amino acid protein. The CARKL protein contains motifs showing weak similarity to 2 domains of the FGGY family of carbohydrate kinases. It does not appear to contain a signal sequence, suggesting that it is localized in the cytoplasm. Northern blot analysis detected expression of a 3.9-kb CARKL transcript predominantly in liver, kidney, and pancreas, with weaker expression in heart, placenta, brain, and lung. Additionally, a 2.7-kb transcript was detected in liver and, to a lesser extent, in heart. By sequence analysis, Touchman et al. (2000) determined that the CARKL gene maps within the telomeric end of a 57-kb segment on 17p13 that is commonly deleted in cystinosis. They hypothesized that CARKL may be a modifier for the cystinosis phenotype.

[20008] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20009] Touchman, J. W.; Anikster, Y.; Dietrich, N. L.; Braden

Maduro, V. V.; McDowell, G.; Shotelersuk, V.; Bouffard, G. G.; Beckstrom-Sternberg, S. M.; Gahl, W. A.; Green, E. D. : The genomic region encompassing the nephropathic cystinosis gene (CTNS): complete sequencing of a 200-kb segment and discovery of a novel gene within the common cystinosis-causing deletion. *Genome Res.* 10: 165–173, 2000. ; and

[20010] Phornphutkul, C.; Anikster, Y.; Huizing, M.; Braun, P.; Brodie, C.; Chou, J. Y.; Gahl, W. A. : The promoter of a lysosomal membrane transporter gene, CTNS, binds Sp-1, shares sequences.

[20011] Further studies establishing the function and utilities of CARKL are found in John Hopkins OMIM database record ID 605060, and in cited publications numbered 503 and 9434 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Glutaminase (GLS, Accession NM\_014905) is another VGAM419 host target gene. GLS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLS BINDING SITE, designated SEQ ID:17112,

to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20012] Another function of VGAM419 is therefore inhibition of Glutaminase (GLS, Accession NM\_014905). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLS. Potassium Voltage-gated Channel, Delayed-rectifier, Subfamily S, Member 2 (KCNS2, Accession XM\_043106) is another VGAM419 host target gene. KCNS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNS2 BINDING SITE, designated SEQ ID:33896, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20013] Another function of VGAM419 is therefore inhibition of Potassium Voltage-gated Channel, Delayed-rectifier, Subfamily S, Member 2 (KCNS2, Accession XM\_043106), a gene which mediates the voltage-dependent potassium ion permeability of excitable membranes. Accordingly,



utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNS2. The function of KCNS2 has been established by previous studies. See KCNS1 (OMIM Ref. No. 602905). By searching an expressed sequence tag (EST) database with the peptide sequence of the silent Kv8.1 alpha subunit, Salinas et al. (1997) identified human cDNAs encoding KCNS2, which they called Kv9.2. Using these ESTs, the authors isolated a mouse Kcns2 cDNA from a brain cDNA library. The predicted 477-amino acid Kcns2 protein has all of the structural characteristics of an outward rectifier Kv alpha subunit, namely 6 transmembrane domains, a transmembrane region with 5 positively charged amino acids, and a conserved pore-forming region. Several putative phosphorylation sites are located in the cytoplasmic regions. Northern blot analysis showed that Kcns2 is expressed only in the brain. In situ hybridization detected high levels of Kcns2 mRNA in the olfactory bulb, cerebral cortex, hippocampal formation, habenula, basolateral amygdaloid nuclei, and cerebellum; expression was also found in the retina and spinal cord. Salinas et al. (1997) demonstrated that Kcns2 does not have potassium channel activity by itself but can modulate the activities of the

Kv2.1 (see OMIM Ref. No. KCNB1; 600397) and Kv2.2 alpha subunits. By fluorescence in situ hybridization and radiation hybrid mapping, Banfi et al. (1996) mapped an EST (GenBank R19352) corresponding to the human KCNS2 gene (Salinas et al., 1997) to 8q22.

[20014] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20015] Banfi, S.; Borsani, G.; Rossi, E.; Bernard, L.; Guffanti, A.; Rubboli, F.; Marchitello, A.; Giglio, S.; Coluccia, E.; Zollo, M.; Zuffardi, O.; Ballabio, A. : Identification and mapping of human cDNAs homologous to Drosophila mutant genes through EST database searching. Nature Genet. 13: 167-174, 1996. ; and

[20016] Salinas, M.; Duprat, F.; Heurteaux, C.; Hugnot, J.-P.; Lazdunski, M. : New modulatory alpha subunits for mammalian Shab K(+) channels. J. Biol. Chem. 272: 24371-24379, 1997.

[20017] Further studies establishing the function and utilities of KCNS2 are found in John Hopkins OMIM database record ID 602906, and in cited publications numbered 6021 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Moesin (MSN, Ac-

cession XM\_013042) is another VGAM419 host target gene. MSN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSN BINDING SITE, designated SEQ ID:30230, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20018] Another function of VGAM419 is therefore inhibition of Moesin (MSN, Accession XM\_013042), a gene which may have a role linking the cytoskeleton to the plasma membrane. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSN. The function of MSN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM248. Neural Retina Leucine Zipper (NRL, Accession NM\_006177) is another VGAM419 host target gene. NRL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRL BINDING SITE, designated SEQ ID:12839, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20019] Another function of VGAM419 is therefore inhibition of Neural Retina Leucine Zipper (NRL, Accession NM\_006177), a gene which has a basic motif and a leucine zipper domain similar to jun and fos. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRL. The function of NRL has been established by previous studies. Farjo et al. (1997) determined the complete sequence of the human NRL gene, identified a polymorphic (CA)<sub>n</sub> repeat (identical to D14S64) within an NRL-containing cosmid, and refined the location of the NRL gene by linkage analysis. Since a locus for autosomal recessive retinitis pigmentosa was thought to map to 14q11 in Sardinian families (Wright et al., 1995), and because mutations in rhodopsin (OMIM Ref. No. 180380), a gene regulated by the NRL protein, cause RP, NRL was considered a valid candidate gene for retinopathies. In a panel of patients representing independent families with inherited

retinal degeneration, Farjo et al. (1997) sequenced genomic PCR products of the NRL gene and of the rhodopsin–NRL response element. No causative mutations were identified. Animal model experiments lend further support to the function of NRL. Mears et al. (2001) generated mice with deletion of the NRL gene. *Nrl*  $-/-$  mice had complete loss of rod function and supernormal cone function, mediated by S cones. The photoreceptors in the *Nrl*  $-/-$  retina had cone-like nuclear morphology and short, sparse outer segments with abnormal disks. Analysis of retinal gene expression confirmed the apparent functional transformation of rods into S cones in the *Nrl*  $-/-$  retina. Mears et al. (2001) suggested that NRL acts as a molecular switch during rod–cell development by directly modulating rod-specific genes while simultaneously inhibiting the S-cone pathway through the activation of NR2E3 (OMIM Ref. No. 604485).

[20020] It is appreciated that the abovementioned animal model for NRL is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20021] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [20022] Farjo, Q.; Jackson, A.; Pieke-Dahl, S.; Scott, K.; Kimberling, W. J.; Sieving, P. A.; Richards, J. E.; Swaroop, A. : Human bZIP transcription factor gene NRL: structure, genomic sequence, and fine linkage mapping at 14q11.2 and negative mutation analysis in patients with retinal degeneration. *Genomics* 45: 395–401, 1997. ; and
- [20023] Mears, A. J.; Kondo, M.; Swain, P. K.; Takada, Y.; Bush, R. A.; Saunders, T. L.; Sieving, P. A.; Swaroop, A. : Nrl is required for rod photoreceptor development. *Nature Genet.* 29: 447–45.
- [20024] Further studies establishing the function and utilities of NRL are found in John Hopkins OMIM database record ID 162080, and in cited publications numbered 12720–12730 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphorylase Kinase, Beta (PHKB, Accession NM\_000293) is another VGAM419 host target gene. PHKB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PHKB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

PHKB BINDING SITE, designated SEQ ID:5838, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20025] Another function of VGAM419 is therefore inhibition of Phosphorylase Kinase, Beta (PHKB, Accession NM\_000293). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PHKB. RAN Binding Protein 9 (RANBP9, Accession NM\_005493) is another VGAM419 host target gene. RANBP9 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RANBP9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RANBP9 BINDING SITE, designated SEQ ID:11996, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20026] Another function of VGAM419 is therefore inhibition of RAN Binding Protein 9 (RANBP9, Accession NM\_005493), a gene which is involved in microtubule nucleation. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with RANBP9. The function of RANBP9 has been established by previous studies. With the 2-hybrid method using human RAN (OMIM Ref. No. 601179) as bait, Nakamura et al. (1998) isolated a novel human protein with a molecular mass of 55 kD, which they called RANBPM. The cDNA is 2.8 kb in length and encodes a protein of 500 amino acid residues. Mouse, hamster, and human RANBPM are identical. The C-terminal half of the *S. cerevisiae* gene YGL227w is 30% identical to RANBPM. Immunoblotting analysis using antibodies against RANBPM revealed that RANBPM was localized within the centrosome throughout the cell cycle. Overexpression of RANBPM produced multiple spots which were colocalized with gamma-tubulin (OMIM Ref. No. 191135) and acted as ectopic microtubule nucleation sites, resulting in a reorganization of the microtubule network. RANBPM cosedimented with centrosomal fractions by sucrose-density gradient centrifugation. Microtubule aster formation was inhibited by both anti-RANBPM antibodies and nonhydrolyzable RAN-GTP (see OMIM Ref. No. 602362). RANBPM specifically interacted with RAN-GTP in a 2-hybrid assay. RANBPM is localized within the central part of microtubule asters. Nakamura et al. (1998)



demonstrated that RANBPM is involved in microtubule nucleation, and suggested that RAN regulates the centrosome through RANBPM. Nishitani et al. (2001) determined that the 55-kD RANBP9 is a truncated protein. They cloned the full-length RANBP9 cDNA by PCR from a HeLa cell library and found that it encodes a deduced 729-amino acid protein with a calculated molecular mass of 79 kD. RANBP9 contains long stretches of proline within the N terminus, and a glutamine stretch following the first proline stretch. Human and mouse RANBP9 share greater than 96% sequence identity. Western blot analysis of transfected cells revealed a protein with an apparent molecular mass of 90 kD. Unlike the truncated protein, the full-length protein does not show localization within centrosomes, but localizes within the perinuclear region or the nucleus. In mitotic COS-7 cells transfected with RANBP9, fluorescence was observed throughout the cell.

[20027] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20028] Nakamura, M.; Masuda, H.; Horii, J.; Kuma, K.; Yokoyama, N.; Ohba, T.; Nishitani, H.; Miyata, T.; Tanaka, M.; Nishimoto, T. : When overexpressed, a novel centrosomal pro-

tein, RanBPM, causes ectopic microtubule nucleation similar to gamma-tubulin. J. Cell Biol. 143: 1041–1052, 1998.  
; and

[20029] Nishitani, H.; Hirose, E.; Uchimura, Y.; Nakamura, M.; Umeda, M.; Nishii, K.; Mori, N.; Nishimoto, T. : Full-sized RanBPM cDNA encodes a protein possessing a long stretch of proline and.

[20030] Further studies establishing the function and utilities of RANBP9 are found in John Hopkins OMIM database record ID 603854, and in cited publications numbered 7420–7421 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SMG1 (Accession NM\_015092) is another VGAM419 host target gene. SMG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SMG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMG1 BINDING SITE, designated SEQ ID:17481, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20031] Another function of VGAM419 is therefore inhibition of SMG1 (Accession NM\_015092), a gene which acts as the

target for the cell-cycle arrest and immunosuppressive effects. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMG1. The function of SMG1 has been established by previous studies. Denning et al. (2001) found that immunoprecipitates of human kidney cells transfected with wildtype SMG1 were active in autophosphorylation assays and in assays using a general phospho-acceptor as substrate. SMG1 also exhibited a strong preference for  $Mn^{2+}$  over  $Mg^{2+}$  and was inhibited by nanomolar concentrations of wortmannin, similar to findings for other PIK-related kinases. It was not inhibited by rapamycin despite the presence of a putative rapamycin-binding domain. Yamashita et al. (2001) found that both the 400-kD and 430-kD SMG1 proteins immunoprecipitated from HeLa cell lysates were capable of autophosphorylation. By mutation analysis, they determined that asp2331 is required for the intrinsic autophosphorylation activity. They also found that overexpression of SMG1, but not of a kinase-inactive point mutant, caused phosphorylation of specific serine residues in the C-terminal SQ motifs of UPF1/SMG2 (RENT1; 601430), a member of the mRNA surveillance complex. Using coex-

pression and immunoprecipitation assays, they determined that SMG1 associates with other components of the mRNA surveillance complex, UPF2 (OMIM Ref. No. 605529) and UPF3A (OMIM Ref. No. 605530). Wortmannin and caffeine were found to inhibit the kinase activity of SMG1, whereas staurosporine and rapamycin did not. Inhibitors of SMG1 induced the accumulation of truncated p53 in human cancer cell lines.

[20032] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20033] Denning, G.; Jamieson, L.; Maquat, L. E.; Thompson, E. A.; Fields, A. P. : Cloning of a novel phosphatidylinositol kinase-related kinase: characterization of the human SMG-1 RNA surveillance protein. J. Biol. Chem. 276: 22709-22714, 2001. ; and

[20034] Yamashita, A.; Ohnishi, T.; Kashima, I.; Taya, Y.; Ohno, S. : Human SMG-1, a novel phosphatidylinositol 3-kinase-related protein kinase, associates with components of the mRNA surveillan.

[20035] Further studies establishing the function and utilities of SMG1 are found in John Hopkins OMIM database record ID 607032, and in sited publications numbered 5386-5387,

110 and 5137 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tumor Necrosis Factor (ligand) Superfamily, Member 15 (TNFSF15, Accession NM\_005118) is another VGAM419 host target gene. TNFSF15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFSF15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFSF15 BINDING SITE, designated SEQ ID:11602, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20036] Another function of VGAM419 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 15 (TNFSF15, Accession NM\_005118), a gene which acts as an autocrine factor to induce apoptosis in endothelial cells. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFSF15. The function of TNFSF15 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM350. Vanin 1

(VNN1, Accession NM\_004666) is another VGAM419 host target gene. VNN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VNN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VNN1 BINDING SITE, designated SEQ ID:11039, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20037] Another function of VGAM419 is therefore inhibition of Vanin 1 (VNN1, Accession NM\_004666), a gene which may regulate steps in thymus homing and play a role in mammalian sexual development. Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VNN1. The function of VNN1 has been established by previous studies. Hematopoietic precursor cells migrate to the thymus, where they differentiate into mature T lymphocytes. Aurrand-Lions et al. (1996) reported the cDNA cloning and functional analysis of mouse vanin-1 (vascular noninflammatory molecule-1), a novel cell surface molecule that is involved in the thymus homing of bone marrow

cells. Vanin-1 is a glycosylphosphatidylinositol (GPI)-anchored molecule expressed by perivascular thymic stromal cells. Antibody against vanin-1 blocked thymus colonization by hematopoietic progenitor cells in both short- and long-term assays and interfered with lymphostromal cell adhesion. The authors suggested that vanin-1 regulates late adhesion steps of thymus homing under physiologic, noninflammatory conditions. The mammalian sex-determining pathway is controlled by the presence or absence of SRY (OMIM Ref. No. 480000) expression in the embryonic gonad. To identify additional sex-determining or gonadal differentiation genes, Grimmond et al. (2000) screened for genes exhibiting sexually dimorphic patterns of expression in the mouse gonad at 12.5 and 13.5 days postcoitum, after overt gonad differentiation, by comparing complex cDNA probes derived from male and female gonadal tissue at these stages on microarrays constructed from a normalized urogenital ridge library. Using in situ hybridization analysis, they determined that mouse protease nexin-1 (OMIM Ref. No. 177010) and Vnn1 exhibit male-specific expression prior to overt gonadal differentiation and are detected in the somatic portion of the developing gonad, suggesting to

the authors a possible direct link to the testis–determining pathway for both genes.

[20038] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20039] Aurrand–Lions, M.; Galland, F.; Bazin, H.; Zakharyev, V. M.; Imhof, B. A.; Naquet, P. : Vanin–1, a novel GPI–linked perivascular molecule involved in thymus homing. *Immunity* 5: 391–405, 1996. ; and

[20040] Grimmond, S.; Van Hateren, N.; Siggers, P.; Arkell, R.; Larder, R.; Soares, M. B.; de Fatima Bonaldo, M.; Smith, L.; Tymowska–Lalanne, Z.; Wells, C.; Greenfield, A. : Sexually dimorphic ex.

[20041] Further studies establishing the function and utilities of VNN1 are found in John Hopkins OMIM database record ID 603570, and in cited publications numbered 5355–5356, 1 and 5357–5358 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Accession NM\_080551) is another VGAM419 host target gene. AP1GBP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AP1GBP1, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP1GBP1 BINDING SITE, designated SEQ ID:27881, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20042] Another function of VGAM419 is therefore inhibition of AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Accession NM\_080551). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP1GBP1. BC022889 (Accession XM\_096964) is another VGAM419 host target gene. BC022889 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BC022889, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BC022889 BINDING SITE, designated SEQ ID:40687, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20043] Another function of VGAM419 is therefore inhibition of BC022889 (Accession XM\_096964). Accordingly, utilities

of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BC022889. C1q and Tumor Necrosis Factor Related Protein 2 (C1QTNF2, Accession NM\_031908) is another VGAM419 host target gene. C1QTNF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1QTNF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1QTNF2 BINDING SITE, designated SEQ ID:25653, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20044] Another function of VGAM419 is therefore inhibition of C1q and Tumor Necrosis Factor Related Protein 2 (C1QTNF2, Accession NM\_031908). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1QTNF2. Chromosome 20 Open Reading Frame 12 (C20orf12, Accession NM\_018152) is another VGAM419 host target gene. C20orf12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf12, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf12 BINDING SITE, designated SEQ ID:19962, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20045] Another function of VGAM419 is therefore inhibition of Chromosome 20 Open Reading Frame 12 (C20orf12, Accession NM\_018152). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf12. Chromosome 20 Open Reading Frame 177 (C20orf177, Accession XM\_030726) is another VGAM419 host target gene. C20orf177 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf177, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf177 BINDING SITE, designated SEQ ID:31130, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20046] Another function of VGAM419 is therefore inhibition of

Chromosome 20 Open Reading Frame 177 (C20orf177, Accession XM\_030726). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf177. Cullin 4A (CUL4A, Accession NM\_003589) is another VGAM419 host target gene. CUL4A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CUL4A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CUL4A BINDING SITE, designated SEQ ID:9642, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20047] Another function of VGAM419 is therefore inhibition of Cullin 4A (CUL4A, Accession NM\_003589). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CUL4A. Deiodinase, Iodothyronine, Type II (DIO2, Accession NM\_013989) is another VGAM419 host target gene. DIO2 BINDING SITE1 and DIO2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DIO2, corresponding to HOST TAR-

GET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DIO2 BINDING SITE1 and DIO2 BINDING SITE2, designated SEQ ID:15172 and SEQ ID:6461 respectively, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20048] Another function of VGAM419 is therefore inhibition of Deiodinase, Iodothyronine, Type II (DIO2, Accession NM\_013989). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIO2. FLJ12660 (Accession NM\_025152) is another VGAM419 host target gene. FLJ12660 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12660, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12660 BINDING SITE, designated SEQ ID:24788, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20049] Another function of VGAM419 is therefore inhibition of

FLJ12660 (Accession NM\_025152). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12660. FLJ12876 (Accession NM\_022754) is another VGAM419 host target gene. FLJ12876 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12876, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12876 BINDING SITE, designated SEQ ID:22988, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20050] Another function of VGAM419 is therefore inhibition of FLJ12876 (Accession NM\_022754). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12876. FLJ20006 (Accession NM\_017618) is another VGAM419 host target gene. FLJ20006 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20006, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ20006 BINDING SITE, designated SEQ ID:19120, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20051] Another function of VGAM419 is therefore inhibition of FLJ20006 (Accession NM\_017618). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20006. FLJ21240 (Accession NM\_024847) is another VGAM419 host target gene. FLJ21240 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21240, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21240 BINDING SITE, designated SEQ ID:24281, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20052] Another function of VGAM419 is therefore inhibition of FLJ21240 (Accession NM\_024847). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21240. KIAA0255 (Accession NM\_014742) is another VGAM419

host target gene. KIAA0255 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0255 BINDING SITE, designated SEQ ID:16414, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20053] Another function of VGAM419 is therefore inhibition of KIAA0255 (Accession NM\_014742). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0255. KIAA0268 (Accession XM\_046126) is another VGAM419 host target gene. KIAA0268 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0268 BINDING SITE, designated SEQ ID:34689, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.



[20054] Another function of VGAM419 is therefore inhibition of KIAA0268 (Accession XM\_046126). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0268. KIAA1126 (Accession XM\_050325) is another VGAM419 host target gene. KIAA1126 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1126, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1126 BINDING SITE, designated SEQ ID:35612, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20055] Another function of VGAM419 is therefore inhibition of KIAA1126 (Accession XM\_050325). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1126. KIAA1473 (Accession XM\_047550) is another VGAM419 host target gene. KIAA1473 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1473, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1473 BINDING SITE, designated SEQ ID:34998, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20056] Another function of VGAM419 is therefore inhibition of KIAA1473 (Accession XM\_047550). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1473. KIAA1649 (Accession XM\_040095) is another VGAM419 host target gene. KIAA1649 BINDING SITE1 and KIAA1649 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KIAA1649, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1649 BINDING SITE1 and KIAA1649 BINDING SITE2, designated SEQ ID:33255 and SEQ ID:26103 respectively, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20057] Another function of VGAM419 is therefore inhibition of KIAA1649 (Accession XM\_040095). Accordingly, utilities

of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1649. Mitochondrial Ribosomal Protein L35 (MRPL35, Accession NM\_016622) is another VGAM419 host target gene. MRPL35 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MRPL35, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MRPL35 BINDING SITE, designated SEQ ID:18734, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20058] Another function of VGAM419 is therefore inhibition of Mitochondrial Ribosomal Protein L35 (MRPL35, Accession NM\_016622). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MRPL35. PDZ Domain Containing 2 (PDZD2, Accession XM\_087705) is another VGAM419 host target gene. PDZD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDZD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDZD2 BINDING SITE, designated SEQ ID:39399, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20059] Another function of VGAM419 is therefore inhibition of PDZ Domain Containing 2 (PDZD2, Accession XM\_087705). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDZD2. PRO0478 (Accession NM\_014129) is another VGAM419 host target gene. PRO0478 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO0478, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0478 BINDING SITE, designated SEQ ID:15398, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20060] Another function of VGAM419 is therefore inhibition of PRO0478 (Accession NM\_014129). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PRO0478. SARM (Accession NM\_015077) is another VGAM419 host target gene. SARM BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SARM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SARM BINDING SITE, designated SEQ ID:17452, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20061] Another function of VGAM419 is therefore inhibition of SARM (Accession NM\_015077). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SARM. Sperm Specific Antigen 2 (SSFA2, Accession XM\_057458) is another VGAM419 host target gene. SSFA2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SSFA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSFA2 BINDING SITE, designated SEQ ID:36515, to the nu-

cleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20062] Another function of VGAM419 is therefore inhibition of Sperm Specific Antigen 2 (SSFA2, Accession XM\_057458). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSFA2. Tripartite Motif-containing 22 (TRIM22, Accession NM\_006074) is another VGAM419 host target gene. TRIM22 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM22, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM22 BINDING SITE, designated SEQ ID:12719, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20063] Another function of VGAM419 is therefore inhibition of Tripartite Motif-containing 22 (TRIM22, Accession NM\_006074). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM22. Zinc Finger Protein 347 (ZNF347, Accession NM\_032584) is another

VGAM419 host target gene. ZNF347 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF347, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF347 BINDING SITE, designated SEQ ID:26320, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20064] Another function of VGAM419 is therefore inhibition of Zinc Finger Protein 347 (ZNF347, Accession NM\_032584). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF347. LOC119504 (Accession XM\_058400) is another VGAM419 host target gene. LOC119504 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC119504, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC119504 BINDING SITE, designated SEQ ID:36616, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3130.

[20065] Another function of VGAM419 is therefore inhibition of LOC119504 (Accession XM\_058400). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC119504. LOC126382 (Accession XM\_072027) is another VGAM419 host target gene. LOC126382 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC126382, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126382 BINDING SITE, designated SEQ ID:37456, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20066] Another function of VGAM419 is therefore inhibition of LOC126382 (Accession XM\_072027). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126382. LOC128977 (Accession XM\_059313) is another VGAM419 host target gene. LOC128977 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC128977, cor-



responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC128977 BINDING SITE, designated SEQ ID:36948, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20067] Another function of VGAM419 is therefore inhibition of LOC128977 (Accession XM\_059313). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC128977. LOC131744 (Accession XM\_067529) is another VGAM419 host target gene. LOC131744 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC131744, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC131744 BINDING SITE, designated SEQ ID:37359, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20068] Another function of VGAM419 is therefore inhibition of LOC131744 (Accession XM\_067529). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC131744. LOC144465 (Accession XM\_084874) is another VGAM419 host target gene. LOC144465 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144465 BINDING SITE, designated SEQ ID:37753, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20069] Another function of VGAM419 is therefore inhibition of LOC144465 (Accession XM\_084874). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144465. LOC145216 (Accession XM\_096730) is another VGAM419 host target gene. LOC145216 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145216, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145216 BINDING SITE, designated SEQ ID:40510, to

the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20070] Another function of VGAM419 is therefore inhibition of LOC145216 (Accession XM\_096730). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145216. LOC148894 (Accession XM\_097542) is another VGAM419 host target gene. LOC148894 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148894 BINDING SITE, designated SEQ ID:40921, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20071] Another function of VGAM419 is therefore inhibition of LOC148894 (Accession XM\_097542). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148894. LOC148932 (Accession XM\_086372) is another VGAM419 host target gene. LOC148932 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC148932, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148932 BINDING SITE, designated SEQ ID:38625, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20072] Another function of VGAM419 is therefore inhibition of LOC148932 (Accession XM\_086372). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148932. LOC149113 (Accession XM\_086425) is another VGAM419 host target gene. LOC149113 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149113, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149113 BINDING SITE, designated SEQ ID:38642, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20073] Another function of VGAM419 is therefore inhibition of LOC149113 (Accession XM\_086425). Accordingly, utilities

of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149113. LOC150630 (Accession XM\_097931) is another VGAM419 host target gene. LOC150630 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150630, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150630 BINDING SITE, designated SEQ ID:41244, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20074] Another function of VGAM419 is therefore inhibition of LOC150630 (Accession XM\_097931). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150630. LOC154403 (Accession XM\_087919) is another VGAM419 host target gene. LOC154403 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154403, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC154403 BINDING SITE, designated SEQ ID:39470, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20075] Another function of VGAM419 is therefore inhibition of LOC154403 (Accession XM\_087919). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154403. LOC154992 (Accession XM\_088106) is another VGAM419 host target gene. LOC154992 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154992, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154992 BINDING SITE, designated SEQ ID:39520, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20076] Another function of VGAM419 is therefore inhibition of LOC154992 (Accession XM\_088106). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154992. LOC196812 (Accession XM\_116868) is another VGAM419 host target gene. LOC196812 BINDING

SITE is HOST TARGET binding site found in the 3` un-translated region of mRNA encoded by LOC196812, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196812 BINDING SITE, designated SEQ ID:43140, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20077] Another function of VGAM419 is therefore inhibition of LOC196812 (Accession XM\_116868). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196812. LOC199858 (Accession XM\_114040) is another VGAM419 host target gene. LOC199858 BINDING SITE is HOST TARGET binding site found in the 5` un-translated region of mRNA encoded by LOC199858, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199858 BINDING SITE, designated SEQ ID:42643, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20078] Another function of VGAM419 is therefore inhibition of

LOC199858 (Accession XM\_114040). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199858. LOC201868 (Accession XM\_114393) is another VGAM419 host target gene. LOC201868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201868 BINDING SITE, designated SEQ ID:42923, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20079] Another function of VGAM419 is therefore inhibition of LOC201868 (Accession XM\_114393). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201868. LOC201911 (Accession XM\_117339) is another VGAM419 host target gene. LOC201911 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201911, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-



illustrates the complementarity of the nucleotide sequences of LOC201911 BINDING SITE, designated SEQ ID:43391, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20080] Another function of VGAM419 is therefore inhibition of LOC201911 (Accession XM\_117339). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201911. LOC219722 (Accession XM\_167593) is another VGAM419 host target gene. LOC219722 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219722, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219722 BINDING SITE, designated SEQ ID:44713, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20081] Another function of VGAM419 is therefore inhibition of LOC219722 (Accession XM\_167593). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219722. LOC221431 (Accession XM\_166380) is an-

other VGAM419 host target gene. LOC221431 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221431, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221431 BINDING SITE, designated SEQ ID:44226, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20082] Another function of VGAM419 is therefore inhibition of LOC221431 (Accession XM\_166380). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221431. LOC254531 (Accession XM\_170773) is another VGAM419 host target gene. LOC254531 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254531, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254531 BINDING SITE, designated SEQ ID:45541, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20083] Another function of VGAM419 is therefore inhibition of LOC254531 (Accession XM\_170773). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254531. LOC90594 (Accession XM\_032820) is another VGAM419 host target gene. LOC90594 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC90594, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90594 BINDING SITE, designated SEQ ID:31775, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20084] Another function of VGAM419 is therefore inhibition of LOC90594 (Accession XM\_032820). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90594. LOC90918 (Accession XM\_034863) is another VGAM419 host target gene. LOC90918 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC90918, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90918 BINDING SITE, designated SEQ ID:32178, to the nucleotide sequence of VGAM419 RNA, herein designated VGAM RNA, also designated SEQ ID:3130.

[20085] Another function of VGAM419 is therefore inhibition of LOC90918 (Accession XM\_034863). Accordingly, utilities of VGAM419 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90918. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 420 (VGAM420) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20086] VGAM420 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM420 was detected is described hereinabove with reference to Figs. 1–8.

[20087] VGAM420 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Papillomavirus Type 39. VGAM420 host target gene, herein designated

VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20088] VGAM420 gene encodes a VGAM420 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM420 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM420 precursor RNA is designated SEQ ID:406, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:406 is located at position 5287 relative to the genome of Human Papillomavirus Type 39.

[20089] VGAM420 precursor RNA folds onto itself, forming VGAM420 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20090] An enzyme complex designated DICER COMPLEX, `dices` the VGAM420 folded precursor RNA into VGAM420 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM420 RNA is designated SEQ ID:3131, and is provided hereinbelow with reference to the sequence listing part.

[20091] VGAM420 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM420 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM420 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20092] VGAM420 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM420 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM420 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM420 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM420 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20093] The complementary binding of VGAM420 RNA, herein designated VGAM RNA, to host target binding sites on VGAM420 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM420 host target RNA into VGAM420 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[20094] It is appreciated that VGAM420 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM420 host target genes. The mRNA of each one of this plurality of VGAM420 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM420 RNA, herein designated VGAM RNA, and which when bound by VGAM420 RNA causes inhibition of translation of respective one or more VGAM420 host target proteins.

[20095] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM420 gene, herein designated VGAM GENE, on one or more VGAM420 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-



pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20096] It is yet further appreciated that a function of VGAM420 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of viral infection by Human Papillomavirus Type 39. Specific functions, and accordingly utilities, of VGAM420 correlate with, and may be deduced from, the identity of the host target genes which VGAM420 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20097] Nucleotide sequences of the VGAM420 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM420 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM420 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM420 are further described hereinbelow with reference to Table 1.

[20098] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM420 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM420 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20099] As mentioned hereinabove with reference to Fig. 1, a function of VGAM420 gene, herein designated VGAM is inhibition of expression of VGAM420 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM420 correlate with, and may be deduced from, the identity of the target genes which VGAM420 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20100] Contactin 3 (plasmacytoma associated) (CNTN3, Accession XM\_039627) is a VGAM420 host target gene. CNTN3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNTN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNTN3 BINDING SITE, designated SEQ ID:33131, to the nucleotide sequence of VGAM420 RNA, herein designated

VGAM RNA, also designated SEQ ID:3131.

[20101] A function of VGAM420 is therefore inhibition of Contactin 3 (plasmacytoma associated) (CNTN3, Accession XM\_039627), a gene which may play a role in the initial growth and guidance of axons. Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNTN3. The function of CNTN3 has been established by previous studies. Pang, a mouse gene encoding a neuronal adhesion molecule, was isolated as a plasmacytoma-specific transcript using an RT-PCR-based strategy in an attempt to isolate Myc-like genes in murine plasmacytomas (Connelly et al., 1994). Pang is a member of the immunoglobulin/fibronectin superfamily of adhesion molecules; its closest relatives, TAG1 (OMIM Ref. No. 190197) and contactin 1 (OMIM Ref. No. 600016), promote axon growth and migration. The normal site of Pang expression is the brain, where it is detected as 4.0- and 6.1-kb RNAs on Northern blots; Pang is not detected in other normal tissues. Abnormally sized Pang transcripts were uniquely found in murine plasmacytomas, where it is ectopically activated by intracisternal A-type particle long terminal repeats. Mock et al. (1996) mapped the Pang

gene to mouse chromosome 6 by somatic cell hybrid analysis and further positioned it on the chromosome between Wnt7a and Pcp1. Southern blot analysis of human-rodent somatic cell hybrids together with predictions from the mouse map location indicated that human PANG is located at 3p26

[20102] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20103] Connelly, M. A.; Grady, R. C.; Mushinski, J. F.; Marcu, K. B. : PANG, a gene encoding a neuronal glycoprotein, is ectopically activated by intracisternal A-type particle long terminal repeats in murine plasmacytomas. Proc. Nat. Acad. Sci. 91: 1337-1341, 1994. ; and

[20104] Mock, B. A.; Connelly, M. A.; McBride, O. W.; Kozak, C. A.; Marcu, K. B. : Plasmacytoma-associated neuronal glycoprotein, Pang, maps to mouse chromosome 6 and human chromosome 3. Genomic.

[20105] Further studies establishing the function and utilities of CNTN3 are found in John Hopkins OMIM database record ID 601325, and in cited publications numbered 9388-9389 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Heme

Oxygenase (decycling) 1 (HMOX1, Accession NM\_002133) is another VGAM420 host target gene. HMOX1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HMOX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HMOX1 BINDING SITE, designated SEQ ID:7909, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20106] Another function of VGAM420 is therefore inhibition of Heme Oxygenase (decycling) 1 (HMOX1, Accession NM\_002133). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HMOX1. Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437) is another VGAM420 host target gene. NCOA4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NCOA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA4 BINDING SITE, designated SEQ ID:11921, to the nucleotide se-

quence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20107] Another function of VGAM420 is therefore inhibition of Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437), a gene which Binds and activates androgen receptor (AR) in ligand-dependent manner. Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA4. The function of NCOA4 has been established by previous studies. The PTC3 oncogene (RET/PTC3) is an activated form of the RET protooncogene (OMIM Ref. No. 164761), which is frequently rearranged in papillary thyroid carcinoma (OMIM Ref. No. 188550). RET/PTC3 results from a structural rearrangement between the ELE1 and RET genes (Bongarzone et al., 1994), and has been observed in both sporadic and radiation-associated post-Chernobyl papillary thyroid carcinoma. To understand the molecular basis that predisposes RET and ELE1 genes to be recurrent targets of 'illegitimate' recombination, Bongarzone et al. (1997) examined the genomic regions containing the ELE1/RET breakpoints in 6 Italian sporadic, RET/PTC3-positive tumors and 3 radiation-associated tumors from children living in areas contaminated by the

Chernobyl accident; the latter tumors also expressed RET/PTC3 oncogene. They found that the breakpoints in both genes clustered in regions that they designated ELE1-bcr (OMIM Ref. No. 1.8 kb) and RET-bcr (OMIM Ref. No. 1.9 kb). In all sporadic tumors and in 1 post-Chernobyl tumor, the ELE1/RET recombination corresponded with short sequences of homology (3 to 7 bp) between the 2 rearranging genes. In addition, Bongarzone et al. (1997) observed an interesting distribution of the post-Chernobyl breakpoints in ELE1-bcr located within an Alu element, or between 2 close Alu elements, and always in AT-rich regions. In the case of the ELE1/RET fusion gene, the 5-prime end of ELE1 is fused to the tyrosine kinase portion of the RET gene. See 601985 for discussion of the PTC1 chimeric oncogene. Androgen receptor (AR; 313700) is a transcriptional factor that belongs to the steroid receptor superfamily based on its structural similarities. Yeh and Chang (1996) noted that members of this family are characterized by 3 major structural regions: a variable amino-terminal domain, a highly conserved cysteine-rich DNA-binding domain, and a carboxyl-terminal ligand-binding domain. When bound to androgens and a cis-acting androgen-responsive element, AR can up- or

down-regulate the expression of androgen target genes through a complicated process that may require other adaptors or coactivators. The fundamental issue in the regulation of steroid hormones is the question of how specific transcription can be achieved in vivo when several receptors, such as AR, glucocorticoid receptor (OMIM Ref. No. 138040), and progesterone receptor (OMIM Ref. No. 607311) can recognize the same DNA sequence. It had been speculated that some accessory factors may selectively interact with the androgen receptor to determine the specificity of AR target gene activation. Using a yeast 2-hybrid system, Yeh and Chang (1996) cloned and characterized a specific AR coactivator. They designated the coactivator ARA(70). The cDNA they isolated encodes a 614-amino acid polypeptide with a predicted molecular weight of 70 kD. The predicted protein shares 99% homology with that encoded by a cDNA clone called RET-fused gene (RFG) that was isolated previously from human thyroid by Santoro et al. (1994). Yeh and Chang (1996) showed that ARA(70) is a ligand-dependent AR-associated protein which functions in human prostate cancer cells as an activator to enhance AR transcriptional activity 10-fold in the presence of dihydrotestosterone or



testosterone, but not hydroxyflutamide. ARA(70) induced only slightly the transcriptional activity of other steroid receptors such as estrogen receptor (OMIM Ref. No. 133430) in human prostate cancer cells.

[20108] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20109] Bongarzone, I.; Butti, M. G.; Fugazzola, L.; Pacini, F.; Pinchera, A.; Vorontsova, T. V.; Demidchik, E. P.; Pierotti, M. A. : Comparison of the breakpoint regions of ELE1 and RET genes involved in the generation of RET/PTC3 onco-gene in sporadic and in radiation-associated papillary thyroid carcinomas. Genomics 42: 252–259, 1997. ; and

[20110] Lim, H. N.; Hawkins, J. R.; Hughes, I. A. : Genetic evidence to exclude the androgen receptor co-factor, ARA70 (NCOA4) as a candidate gene for the causation of under-masculinised genital.

[20111] Further studies establishing the function and utilities of NCOA4 are found in John Hopkins OMIM database record ID 601984, and in cited publications numbered 10594–8896 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neurogenic Differentiation 1 (NEUROD1, Accession

NM\_002500) is another VGAM420 host target gene. NEUROD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEUROD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEUROD1 BINDING SITE, designated SEQ ID:8322, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20112] Another function of VGAM420 is therefore inhibition of Neurogenic Differentiation 1 (NEUROD1, Accession NM\_002500), a gene which acts as a differentiation factor during neurogenesis. Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEUROD1. The function of NEUROD1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM130. Phosphodiesterase 4D, CAMP-specific (phosphodiesterase E3 dunce homolog, Drosophila) (PDE4D, Accession XM\_056815) is another VGAM420 host target gene. PDE4D BINDING SITE is HOST TARGET binding

site found in the 3' untranslated region of mRNA encoded by PDE4D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDE4D BINDING SITE, designated SEQ ID:36424, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20113] Another function of VGAM420 is therefore inhibition of Phosphodiesterase 4D, CAMP-specific (phosphodiesterase E3 dunce homolog, Drosophila) (PDE4D, Accession XM\_056815), a gene which has similarity to Drosophila dnc, which is the affected protein in learning and memory mutant dunce. Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDE4D. The function of PDE4D and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM180. Apolipoprotein L, 6 (APOL6, Accession NM\_030641) is another VGAM420 host target gene. APOL6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APOL6,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APOL6 BINDING SITE, designated SEQ ID:24973, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20114] Another function of VGAM420 is therefore inhibition of Apolipoprotein L, 6 (APOL6, Accession NM\_030641). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOL6. DKFZP761L0424 (Accession XM\_166112) is another VGAM420 host target gene. DKFZP761L0424 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP761L0424, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP761L0424 BINDING SITE, designated SEQ ID:43891, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20115] Another function of VGAM420 is therefore inhibition of

DKFZP761L0424 (Accession XM\_166112). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP761L0424. FLJ20312 (Accession NM\_017761) is another VGAM420 host target gene. FLJ20312 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20312, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20312 BINDING SITE, designated SEQ ID:19372, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20116] Another function of VGAM420 is therefore inhibition of FLJ20312 (Accession NM\_017761). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20312. KIAA1950 (Accession XM\_166532) is another VGAM420 host target gene. KIAA1950 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1950, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA1950 BINDING SITE, designated SEQ ID:44481, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20117] Another function of VGAM420 is therefore inhibition of KIAA1950 (Accession XM\_166532). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1950. MGC5391 (Accession NM\_032740) is another VGAM420 host target gene. MGC5391 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC5391, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5391 BINDING SITE, designated SEQ ID:26470, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20118] Another function of VGAM420 is therefore inhibition of MGC5391 (Accession NM\_032740). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5391. RING1 and YY1 Binding Protein (RYBP, Acces-

sion XM\_002853) is another VGAM420 host target gene. RYBP BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RYBP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RYBP BINDING SITE, designated SEQ ID:29907, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also designated SEQ ID:3131.

[20119] Another function of VGAM420 is therefore inhibition of RING1 and YY1 Binding Protein (RYBP, Accession XM\_002853). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RYBP. LOC255533 (Accession XM\_173073) is another VGAM420 host target gene. LOC255533 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC255533, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255533 BINDING SITE, designated SEQ ID:46328, to the nucleotide sequence of VGAM420 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3131.

[20120] Another function of VGAM420 is therefore inhibition of LOC255533 (Accession XM\_173073). Accordingly, utilities of VGAM420 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255533. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 421 (VGAM421) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20121] VGAM421 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM421 was detected is described hereinabove with reference to Figs. 1–8.

[20122] VGAM421 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Papillomavirus Type 39. VGAM421 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20123] VGAM421 gene encodes a VGAM421 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other



miRNA genes, and unlike most ordinary genes, VGAM421 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM421 precursor RNA is designated SEQ ID:407, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:407 is located at position 4323 relative to the genome of Human Papillomavirus Type 39.

[20124] VGAM421 precursor RNA folds onto itself, forming VGAM421 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20125] An enzyme complex designated DICER COMPLEX, `dices` the VGAM421 folded precursor RNA into VGAM421 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM421 RNA is designated SEQ ID:3132, and is provided hereinbelow with reference to the sequence listing part.

[20126] VGAM421 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM421 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM421 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20127] VGAM421 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM421 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM421 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM421 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM421 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20128] The complementary binding of VGAM421 RNA, herein designated VGAM RNA, to host target binding sites on VGAM421 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM421 host target RNA into VGAM421 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20129] It is appreciated that VGAM421 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM421 host target genes. The mRNA of

each one of this plurality of VGAM421 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM421 RNA, herein designated VGAM RNA, and which when bound by VGAM421 RNA causes inhibition of translation of respective one or more VGAM421 host target proteins.

[20130] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM421 gene, herein designated VGAM GENE, on one or more VGAM421 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[20131] It is yet further appreciated that a function of VGAM421 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM421 include diagnosis, prevention and treatment of viral infection by Human Papillomavirus Type 39. Specific functions, and accordingly utilities, of VGAM421 correlate with, and may be deduced from, the identity of the host target genes which VGAM421 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20132] Nucleotide sequences of the VGAM421 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM421 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM421 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM421 are further described hereinbelow with reference to Table 1.

[20133] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM421 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM421 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[20134] As mentioned hereinabove with reference to Fig. 1, a function of VGAM421 gene, herein designated VGAM is inhibition of expression of VGAM421 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM421 correlate with, and may be deduced from, the identity of the target genes which VGAM421 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20135] MADS Box Transcription Enhancer Factor 2, Polypeptide C (myocyte enhancer factor 2C) (MEF2C, Accession NM\_002397) is a VGAM421 host target gene. MEF2C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MEF2C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEF2C BINDING SITE, designated SEQ ID:8210, to the nucleotide sequence of VGAM421 RNA, herein designated VGAM RNA, also designated SEQ ID:3132.

[20136] A function of VGAM421 is therefore inhibition of MADS Box Transcription Enhancer Factor 2, Polypeptide C

(myocyte enhancer factor 2C) (MEF2C, Accession NM\_002397), a gene which regulates muscle-specific and mitogen-inducible genes. Accordingly, utilities of VGAM421 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEF2C. The function of MEF2C and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM386. Sal-like 1 (Drosophila) (SALL1, Accession NM\_002968) is another VGAM421 host target gene. SALL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SALL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SALL1 BINDING SITE, designated SEQ ID:8880, to the nucleotide sequence of VGAM421 RNA, herein designated VGAM RNA, also designated SEQ ID:3132.

[20137] Another function of VGAM421 is therefore inhibition of Sal-like 1 (Drosophila) (SALL1, Accession NM\_002968). Accordingly, utilities of VGAM421 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SALL1. Enabled Homolog (Drosophila)

(ENAH, Accession NM\_018212) is another VGAM421 host target gene. ENAH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ENAH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ENAH BINDING SITE, designated SEQ ID:20126, to the nucleotide sequence of VGAM421 RNA, herein designated VGAM RNA, also designated SEQ ID:3132.

[20138] Another function of VGAM421 is therefore inhibition of Enabled Homolog (Drosophila) (ENAH, Accession NM\_018212). Accordingly, utilities of VGAM421 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ENAH. KIAA0556 (Accession XM\_044632) is another VGAM421 host target gene. KIAA0556 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0556 BINDING SITE, designated SEQ ID:34249, to the nucleotide sequence of VGAM421 RNA,



herein designated VGAM RNA, also designated SEQ ID:3132.

[20139] Another function of VGAM421 is therefore inhibition of KIAA0556 (Accession XM\_044632). Accordingly, utilities of VGAM421 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0556. KIAA0648 (Accession XM\_094043) is another VGAM421 host target gene. KIAA0648 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0648, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0648 BINDING SITE, designated SEQ ID:40220, to the nucleotide sequence of VGAM421 RNA, herein designated VGAM RNA, also designated SEQ ID:3132.

[20140] Another function of VGAM421 is therefore inhibition of KIAA0648 (Accession XM\_094043). Accordingly, utilities of VGAM421 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0648. LOC143465 (Accession XM\_096430) is another VGAM421 host target gene. LOC143465 BINDING SITE is HOST TARGET binding site found in the 5' untranslated

region of mRNA encoded by LOC143465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143465 BINDING SITE, designated SEQ ID:40361, to the nucleotide sequence of VGAM421 RNA, herein designated VGAM RNA, also designated SEQ ID:3132.

[20141] Another function of VGAM421 is therefore inhibition of LOC143465 (Accession XM\_096430). Accordingly, utilities of VGAM421 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143465. LOC147599 (Accession XM\_097253) is another VGAM421 host target gene. LOC147599 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147599, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147599 BINDING SITE, designated SEQ ID:40847, to the nucleotide sequence of VGAM421 RNA, herein designated VGAM RNA, also designated SEQ ID:3132.

[20142] Another function of VGAM421 is therefore inhibition of LOC147599 (Accession XM\_097253). Accordingly, utilities

of VGAM421 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147599. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 422 (VGAM422) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20143] VGAM422 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM422 was detected is described hereinabove with reference to Figs. 1–8.

[20144] VGAM422 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Canine Parvovirus. VGAM422 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20145] VGAM422 gene encodes a VGAM422 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM422 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM422 precursor RNA is designated SEQ ID:408, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:408 is located at position 1869 relative to the genome of Canine Parvovirus.

[20146] VGAM422 precursor RNA folds onto itself, forming VGAM422 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20147] An enzyme complex designated DICER COMPLEX, `dices` the VGAM422 folded precursor RNA into VGAM422 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM422 RNA is designated SEQ ID:3133, and

is provided hereinbelow with reference to the sequence listing part.

[20148] VGAM422 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM422 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM422 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20149] VGAM422 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM422 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM422 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM422 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM422 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20150] The complementary binding of VGAM422 RNA, herein designated VGAM RNA, to host target binding sites on VGAM422 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM422 host target RNA into VGAM422 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20151] It is appreciated that VGAM422 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM422 host target genes. The mRNA of each one of this plurality of VGAM422 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM422 RNA, herein designated VGAM RNA, and which when bound by VGAM422 RNA causes inhibition of translation of respective one or more VGAM422 host target proteins.

[20152] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM422 gene, herein designated VGAM GENE, on one or more VGAM422 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20153] It is yet further appreciated that a function of VGAM422 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM422 include diagnosis, prevention and treatment of viral infection by Canine Parvovirus. Specific functions, and accordingly utilities, of VGAM422 correlate with, and may be deduced from, the identity of the host target genes which VGAM422 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20154] Nucleotide sequences of the VGAM422 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM422 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM422 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM422 are further described hereinbelow with reference to Table 1.

[20155] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM422 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM422 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20156] As mentioned hereinabove with reference to Fig. 1, a



function of VGAM422 gene, herein designated VGAM is inhibition of expression of VGAM422 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM422 correlate with, and may be deduced from, the identity of the target genes which VGAM422 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20157] Pumilio Homolog 1 (Drosophila) (PUM1, Accession NM\_014676) is a VGAM422 host target gene. PUM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PUM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PUM1 BINDING SITE, designated SEQ ID:16147, to the nucleotide sequence of VGAM422 RNA, herein designated VGAM RNA, also designated SEQ ID:3133.

[20158] A function of VGAM422 is therefore inhibition of Pumilio Homolog 1 (Drosophila) (PUM1, Accession NM\_014676), a gene which is a human homolog of the Drosophila Pumilio protein. Accordingly, utilities of VGAM422 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PUM1. The function of PUM1

has been established by previous studies. By sequencing cDNAs randomly selected from a cDNA library derived from the human immature myeloid cell line KG-1, Nagase et al. (1995) isolated a cDNA encoding PUM1, a human homolog of the *Drosophila* Pumilio protein, which they designated KIAA0099. The predicted 1,186-amino acid KIAA0099 protein is 42.1% identical to *Drosophila* Pumilio over an 875-amino acid region . Northern blot analysis detected expression of KIAA0099 in all tissues tested. Wang et al. (2002) determined the structure of the RNA-binding domain of human PUM1 bound to a high-affinity RNA ligand. The RNA binds the concave surface of the molecule, where each of the protein's 8 repeats makes contact with a different RNA base via 3 amino acid side chains at conserved positions. Wang et al. (2002) mutated these 3 side chains in 1 repeat, thereby altering the sequence specificity of PUM1. They concluded that the high affinity and specificity of the PUM homology domain for RNA is achieved using multiple copies of a simple repeated motif.

[20159] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [20160] Nagase, T; Miyajima, N; Tanaka, A.; Sazuka, T.; Seki, N.; Sato, S.; Tabata, S.; Ishikawa, K.; Kawarabayashi, Y.; Kotani, H.; Nomura, N. : Prediction of the coding sequences of unidentified human genes. III. The coding sequences of 40 new genes (KIAA0081–KIAA0120) deduced by analysis of cDNA clones from human cell line KG–1. DNA Res. 2: 37–43, 1995. ; and
- [20161] Wang, X.; McLachlan, J.; Zamore, P. D.; Hall, T. M. T. : Modular recognition of RNA by a human Pumilio–homology domain. Cell 110: 501–512, 2002.
- [20162] Further studies establishing the function and utilities of PUM1 are found in John Hopkins OMIM database record ID 607204, and in cited publications numbered 6726 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SRY (sex determining region Y)–box 13 (SOX13, Accession NM\_005686) is another VGAM422 host target gene. SOX13 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SOX13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOX13 BINDING SITE, designated SEQ ID:12241, to the nucleotide se–

quence of VGAM422 RNA, herein designated VGAM RNA, also designated SEQ ID:3133.

[20163] Another function of VGAM422 is therefore inhibition of SRY (sex determining region Y)-box 13 (SOX13, Accession NM\_005686). Accordingly, utilities of VGAM422 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOX13. Down Syndrome Critical Region Gene 1-like 1 (DSCR1L1, Accession NM\_005822) is another VGAM422 host target gene. DSCR1L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DSCR1L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DSCR1L1 BINDING SITE, designated SEQ ID:12428, to the nucleotide sequence of VGAM422 RNA, herein designated VGAM RNA, also designated SEQ ID:3133.

[20164] Another function of VGAM422 is therefore inhibition of Down Syndrome Critical Region Gene 1-like 1 (DSCR1L1, Accession NM\_005822). Accordingly, utilities of VGAM422 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSCR1L1. Fig. 1

further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 423 (VGAM423) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20165] VGAM423 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM423 was detected is described hereinabove with reference to Figs. 1–8.

[20166] VGAM423 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Canine Parvovirus. VGAM423 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20167] VGAM423 gene encodes a VGAM423 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM423 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM423 precursor RNA is designated SEQ ID:409, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:409 is

located at position 1298 relative to the genome of Canine Parvovirus.

[20168] VGAM423 precursor RNA folds onto itself, forming VGAM423 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20169] An enzyme complex designated DICER COMPLEX, `dices` the VGAM423 folded precursor RNA into VGAM423 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM423 RNA is designated SEQ ID:3134, and is provided hereinbelow with reference to the sequence listing part.

[20170] VGAM423 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM423 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM423 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[20171] VGAM423 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM423 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM423 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM423 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM423 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[20172] The complementary binding of VGAM423 RNA, herein designated VGAM RNA, to host target binding sites on VGAM423 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM423 host target RNA into VGAM423 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20173] It is appreciated that VGAM423 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM423 host target genes. The mRNA of each one of this plurality of VGAM423 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM423 RNA, herein designated VGAM RNA, and which when bound by VGAM423 RNA causes inhibition of translation of respective one or more VGAM423



host target proteins.

[20174] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM423 gene, herein designated VGAM GENE, on one or more VGAM423 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20175] It is yet further appreciated that a function of VGAM423 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM423 include diagnosis, prevention and treatment of viral infection by Canine Parvovirus. Specific

functions, and accordingly utilities, of VGAM423 correlate with, and may be deduced from, the identity of the host target genes which VGAM423 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20176] Nucleotide sequences of the VGAM423 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM423 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM423 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM423 are further described hereinbelow with reference to Table 1.

[20177] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM423 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM423 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20178] As mentioned hereinabove with reference to Fig. 1, a function of VGAM423 gene, herein designated VGAM is inhibition of expression of VGAM423 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM423 correlate with, and may be deduced from, the identity of the target genes which VGAM423 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20179] Component of Oligomeric Golgi Complex 6 (COG6, Accession XM\_053233) is a VGAM423 host target gene. COG6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COG6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COG6 BINDING SITE, designated SEQ ID:36067, to the nucleotide sequence of VGAM423 RNA, herein designated VGAM RNA, also designated SEQ ID:3134.

[20180] A function of VGAM423 is therefore inhibition of Component of Oligomeric Golgi Complex 6 (COG6, Accession XM\_053233), a gene which is critical for the structure and function of the Golgi apparatus. Accordingly, utilities of VGAM423 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COG6. The function of COG6 has been established by previous studies. Multiprotein complexes are key determinants of Golgi apparatus structure and its capacity for intracellular

transport and glycoprotein modification. Several complexes have been identified, including the Golgi transport complex (GTC), the LDLC complex, which is involved in glycosylation reactions, and the SEC34 complex, which is involved in vesicular transport. These 3 complexes are identical and have been termed the conserved oligomeric Golgi (COG) complex, which includes COG6 (Ungar et al., 2002). By SDS-PAGE analysis of bovine brain cytosol, Ungar et al. (2002) identified the 8 subunits of the COG complex. Immunofluorescence microscopy demonstrated that COG1 (LDLB; 606973) colocalizes with COG7 (OMIM Ref. No. 606978), as well as with COG3 (OMIM Ref. No. 606975) and COG5 (OMIM Ref. No. 606821), with a Golgi marker in a perinuclear distribution. Immunoprecipitation analysis showed that all COG subunits interact with COG2 (LDLC; 606974). Ungar et al. (2002) concluded that the COG complex is critical for the structure and function of the Golgi apparatus and can influence intracellular membrane trafficking.

[20181] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20182] Ungar, D.; Oka, T.; Brittle, E. E.; Vasile, E.; Lupashin, V. V.;

Chatterton, J. E.; Heuser, J. E.; Krieger, M.; Waters, M. G. : Characterization of a mammalian Golgi-localized protein complex, COG, that is required for normal Golgi morphology and function. J. Cell Biol. 157: 405–415, 2002. ; and

[20183] Hirosawa, M.; Nagase, T.; Ishikawa, K.; Kikuno, R.; Nomura, N.; Ohara, O. : Characterization of cDNA clones selected by the GeneMark analysis from size-fractionated cDNA libraries from.

[20184] Further studies establishing the function and utilities of COG6 are found in John Hopkins OMIM database record ID 606977, and in cited publications numbered 7480 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protocadherin 19 (PCDH19, Accession XM\_033173) is another VGAM423 host target gene. PCDH19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDH19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDH19 BINDING SITE, designated SEQ ID:31860, to the nucleotide sequence of VGAM423 RNA, herein designated VGAM RNA, also designated SEQ ID:3134.

[20185] Another function of VGAM423 is therefore inhibition of Protocadherin 19 (PCDH19, Accession XM\_033173). Accordingly, utilities of VGAM423 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH19. LOC146108 (Accession XM\_085322) is another VGAM423 host target gene. LOC146108 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146108, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146108 BINDING SITE, designated SEQ ID:38064, to the nucleotide sequence of VGAM423 RNA, herein designated VGAM RNA, also designated SEQ ID:3134.

[20186] Another function of VGAM423 is therefore inhibition of LOC146108 (Accession XM\_085322). Accordingly, utilities of VGAM423 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146108. LOC151126 (Accession XM\_087103) is another VGAM423 host target gene. LOC151126 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151126, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151126 BINDING SITE, designated SEQ ID:39058, to the nucleotide sequence of VGAM423 RNA, herein designated VGAM RNA, also designated SEQ ID:3134.

[20187] Another function of VGAM423 is therefore inhibition of LOC151126 (Accession XM\_087103). Accordingly, utilities of VGAM423 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151126. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 424 (VGAM424) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20188] VGAM424 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM424 was detected is described hereinabove with reference to Figs. 1–8.

[20189] VGAM424 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabies Virus. VGAM424

host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20190] VGAM424 gene encodes a VGAM424 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM424 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM424 precursor RNA is designated SEQ ID:410, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:410 is located at position 5883 relative to the genome of Rabies Virus.

[20191] VGAM424 precursor RNA folds onto itself, forming VGAM424 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20192] An enzyme complex designated DICER COMPLEX, `dices` the VGAM424 folded precursor RNA into VGAM424 RNA,



herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM424 RNA is designated SEQ ID:3135, and is provided hereinbelow with reference to the sequence listing part.

[20193] VGAM424 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM424 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM424 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20194] VGAM424 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM424 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM424 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM424 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM424 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20195] The complementary binding of VGAM424 RNA, herein designated VGAM RNA, to host target binding sites on VGAM424 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM424 host target RNA into VGAM424 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[20196] It is appreciated that VGAM424 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM424 host target genes. The mRNA of each one of this plurality of VGAM424 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM424 RNA, herein designated VGAM RNA, and which when bound by VGAM424 RNA causes inhibition of translation of respective one or more VGAM424 host target proteins.

[20197] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM424 gene, herein designated VGAM GENE, on one or more VGAM424 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20198] It is yet further appreciated that a function of VGAM424 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of viral infection by Rabies Virus. Specific functions, and accordingly utilities, of VGAM424 correlate with, and may be deduced from, the identity of the host target genes which VGAM424 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20199] Nucleotide sequences of the VGAM424 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM424 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM424 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM424 are further described hereinbelow with reference to Table 1.

[20200] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM424 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM424 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20201] As mentioned hereinabove with reference to Fig. 1, a function of VGAM424 gene, herein designated VGAM is inhibition of expression of VGAM424 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM424 correlate with, and may be deduced from, the identity of the target genes which VGAM424 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20202] SUV39H2 (Accession NM\_024670) is a VGAM424 host target gene. SUV39H2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SUV39H2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SUV39H2 BINDING SITE, designated SEQ ID:23974, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ

ID:3135.

[20203] A function of VGAM424 is therefore inhibition of SUV39H2 (Accession NM\_024670), a gene which is involved in gene repression and the modification of position-effect-variation. Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SUV39H2. The function of SUV39H2 has been established by previous studies. O'Carroll et al. (2000) isolated and characterized a murine gene, Suv39h2, that encodes an H3 histone (see OMIM Ref. No. 601128) methyltransferase (OMIM Ref. No. HMTase) with 59% identity to Suv39h1 (OMIM Ref. No. 300254). Although both Suv39h loci displayed overlapping expression profiles during mouse embryogenesis, Suv39h2 transcripts remained specifically expressed in adult testes. Immunolocalization of the Suv39h2 protein during spermatogenesis indicated enriched distribution at the heterochromatin from the leptotene to the round spermatid stage. Moreover, Suv39h2 specifically accumulated with chromatin of the sex chromosomes (XY body), which undergo transcriptional silencing during the first meiotic prophase. These data were consistent with redundant enzymatic roles for Suv39h1 and Suv39h2 during

mouse development and suggested an additional function of the Suv39h2 HMTase in organizing meiotic heterochromatin that may even impart an epigenetic imprint to the male germline. Animal model experiments lend further support to the function of SUV39H2. Peters et al. (2001) generated mice deficient for either Suv39h1 or Suv39h2. These animals displayed normal viability and fertility and did not exhibit apparent phenotypes. The authors subsequently intercrossed Suv39h1  $-/-$  and Suv39h2  $-/-$  mice to generate compound Suv39h mutants that were then used to derive Suv39h double-null mice (Suv39h1  $-/-$  and Suv39h2  $-/-$ ). These mice displayed severely impaired viability and chromosomal instabilities that were associated with an increased tumor risk and perturbed chromosome interactions during male meiosis. These data suggested a crucial role for pericentric H3 histone-lys9 methylation in protecting genome stability and defined the Suv39h HMTases as important epigenetic regulators for mammalian development.

[20204] It is appreciated that the abovementioned animal model for SUV39H2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

- [20205] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [20206] O'Carroll, D.; Scherthan, H.; Peters, A. H. F. M.; Opravil, S.; Haynes, A. R.; Laible, G.; Rea, S.; Schmid, M.; Lebersorger, A.; Jerratsch, M.; Sattler, L.; Mattei, M. G.; Denny, P.; Brown, S. D. M.; Schweizer, D.; Jenuwein, T. : Isolation and characterization of Suv39h2, a second histone H3 methyltransferase gene that displays testis-specific expression. *Molec. Cell. Biol.* 20: 9423–9433, 2000. ; and
- [20207] Peters, A. H. F. M.; O'Carroll, D.; Scherthan, H.; Mechtler, K.; Sauer, S.; Schofer, C.; Weipoltshammer, K.; Pagani, M.; Lachner, M.; Kohlmaier, A.; Opravil, S.; Doyle, M.; Sibilia, M.
- [20208] Further studies establishing the function and utilities of SUV39H2 are found in John Hopkins OMIM database record ID 606503, and in cited publications numbered 610 and 9071 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ13340 (Accession NM\_057175) is another VGAM424 host target gene. FLJ13340 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13340, corresponding to a



HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13340 BINDING SITE, designated SEQ ID:27704, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20209] Another function of VGAM424 is therefore inhibition of FLJ13340 (Accession NM\_057175). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13340. TBDN100 (Accession NM\_025085) is another VGAM424 host target gene. TBDN100 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TBDN100, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBDN100 BINDING SITE, designated SEQ ID:24693, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20210] Another function of VGAM424 is therefore inhibition of TBDN100 (Accession NM\_025085). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with TBDN100. Yes-associated Protein 1, 65kDa (YAP1, Accession NM\_006106) is another VGAM424 host target gene. YAP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by YAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of YAP1 BINDING SITE, designated SEQ ID:12749, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20211] Another function of VGAM424 is therefore inhibition of Yes-associated Protein 1, 65kDa (YAP1, Accession NM\_006106). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with YAP1. LOC143153 (Accession XM\_084440) is another VGAM424 host target gene. LOC143153 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC143153, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143153 BINDING SITE, desig-

nated SEQ ID:37577, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20212] Another function of VGAM424 is therefore inhibition of LOC143153 (Accession XM\_084440). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143153. LOC143154 (Accession XM\_084441) is another VGAM424 host target gene. LOC143154 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143154, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143154 BINDING SITE, designated SEQ ID:37584, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20213] Another function of VGAM424 is therefore inhibition of LOC143154 (Accession XM\_084441). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143154. LOC144571 (Accession XM\_096630) is another VGAM424 host target gene. LOC144571 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144571, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144571 BINDING SITE, designated SEQ ID:40440, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20214] Another function of VGAM424 is therefore inhibition of LOC144571 (Accession XM\_096630). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144571. LOC146346 (Accession XM\_085430) is another VGAM424 host target gene. LOC146346 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146346, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146346 BINDING SITE, designated SEQ ID:38137, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20215] Another function of VGAM424 is therefore inhibition of

LOC146346 (Accession XM\_085430). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146346. LOC219294 (Accession XM\_167566) is another VGAM424 host target gene. LOC219294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219294 BINDING SITE, designated SEQ ID:44685, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20216] Another function of VGAM424 is therefore inhibition of LOC219294 (Accession XM\_167566). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219294. LOC219295 (Accession XM\_167565) is another VGAM424 host target gene. LOC219295 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219295, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC219295 BINDING SITE, designated SEQ ID:44680, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20217] Another function of VGAM424 is therefore inhibition of LOC219295 (Accession XM\_167565). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219295. LOC219790 (Accession XM\_166124) is another VGAM424 host target gene. LOC219790 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219790, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219790 BINDING SITE, designated SEQ ID:43904, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20218] Another function of VGAM424 is therefore inhibition of LOC219790 (Accession XM\_166124). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219790. LOC221687 (Accession XM\_166423) is an-

other VGAM424 host target gene. LOC221687 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221687 BINDING SITE, designated SEQ ID:44303, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20219] Another function of VGAM424 is therefore inhibition of LOC221687 (Accession XM\_166423). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221687. LOC83690 (Accession NM\_031461) is another VGAM424 host target gene. LOC83690 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC83690, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC83690 BINDING SITE, designated SEQ ID:25483, to the nucleotide sequence of VGAM424 RNA, herein designated VGAM RNA, also designated SEQ ID:3135.

[20220] Another function of VGAM424 is therefore inhibition of LOC83690 (Accession NM\_031461). Accordingly, utilities of VGAM424 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC83690. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 425 (VGAM425) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20221] VGAM425 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM425 was detected is described hereinabove with reference to Figs. 1–8.

[20222] VGAM425 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabies Virus. VGAM425 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20223] VGAM425 gene encodes a VGAM425 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM425 precursor RNA does not encode a protein. A nucleotide



sequence identical or highly similar to the nucleotide sequence of VGAM425 precursor RNA is designated SEQ ID:411, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:411 is located at position 8963 relative to the genome of Rabies Virus.

[20224] VGAM425 precursor RNA folds onto itself, forming VGAM425 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20225] An enzyme complex designated DICER COMPLEX, `dices` the VGAM425 folded precursor RNA into VGAM425 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide se-

quence of VGAM425 RNA is designated SEQ ID:3136, and is provided hereinbelow with reference to the sequence listing part.

[20226] VGAM425 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM425 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM425 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20227] VGAM425 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM425 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM425 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM425 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM425 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[20228] The complementary binding of VGAM425 RNA, herein designated VGAM RNA, to host target binding sites on VGAM425 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM425 host target RNA into VGAM425 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20229] It is appreciated that VGAM425 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM425 host target genes. The mRNA of each one of this plurality of VGAM425 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM425 RNA, herein designated VGAM RNA, and which when bound by VGAM425 RNA causes inhibition of translation of respective one or more VGAM425 host target proteins.

[20230] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM425 gene, herein designated VGAM GENE, on one or more VGAM425 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20231] It is yet further appreciated that a function of VGAM425 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of viral infection by Rabies Virus. Specific functions, and accordingly utilities, of VGAM425 correlate with, and may be deduced from, the identity of the host target genes which VGAM425 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20232] Nucleotide sequences of the VGAM425 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM425 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM425 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM425 are further described hereinbelow with reference to Table 1.

[20233] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM425 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM425 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20234] As mentioned hereinabove with reference to Fig. 1, a function of VGAM425 gene, herein designated VGAM is inhibition of expression of VGAM425 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM425 correlate with, and may be deduced from, the identity of the target genes which VGAM425 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20235] Amyloid Beta (A4) Precursor Protein-binding, Family B, Member 2 (Fe65-like) (APBB2, Accession XM\_051782) is a VGAM425 host target gene. APBB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APBB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APBB2 BINDING SITE, designated SEQ ID:35879, to the nucleotide sequence of VGAM425 RNA, herein designated VGAM RNA, also designated SEQ ID:3136.

[20236] A function of VGAM425 is therefore inhibition of Amyloid Beta (A4) Precursor Protein-binding, Family B, Member 2 (Fe65-like) (APBB2, Accession XM\_051782), a gene which Interacts with beta-amyloid precursor protein and with

APLP2. Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APBB2. The function of APBB2 has been established by previous studies. The cytoplasmic domain of the Alzheimer disease locus amyloid protein precursor (APP; 107640) binds 4 human phosphotyrosine-binding (PTB) proteins; see APBA1 (OMIM Ref. No. 602414). By use of a yeast 2-hybrid screening of a human brain cDNA library, McLoughlin and Miller (1996) identified 3 of these proteins: the human homolog of Fe65 (APBB1; 602709), an Fe65-like sequence (APBB2), and an X11-like sequence (APBA2; 602712). From a human fetal brain cDNA library, Guenette et al. (1996) also cloned APBB2 based on its interaction with the carboxy terminus of APP. They showed that the APBB2 protein interacts with another amyloid protein precursor, APLP2 (OMIM Ref. No. 104776), but not with APLP1 (OMIM Ref. No. 104775). The APBB2 gene encodes a 730-amino acid polypeptide that is 51% identical to rat Fe65. Northern blot analysis revealed that APBB2 has widespread expression in human tissues. By use of a radiation hybrid panel, Blanco et al. (1998) mapped the human APBB2 gene to chromosome 4, between the markers D4S405 (OMIM Ref. No. 4.6 cR) and D4S496 (10.1 cR).

[20237] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20238] Blanco, G.; Irving, N. G.; Brown, S. D. M.; Miller, C. C. J.; McLoughlin, D. M. : Mapping of the human and murine X11-like genes (APBA2 and Apba2), the murine Fe65 gene (Apbb1), and the human Fe65-like gene (APBB2): genes encoding phosphotyrosine-binding domain proteins that interact with the Alzheimer's disease amyloid precursor protein. Mammalian Genome 9: 473-475, 1998. ; and

[20239] Guenette, S. Y.; Chen, J.; Jondro, P. D.; Tanzi, R. E. : Association of a novel human FE65-like protein with the cytoplasmic domain of the beta-amyloid precursor protein. Proc. Nat. Acad.

[20240] Further studies establishing the function and utilities of APBB2 are found in John Hopkins OMIM database record ID 602710, and in cited publications numbered 101 and 1119 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010) is another VGAM425 host target gene. NRCAM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRCAM, corresponding to a



HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRCAM BINDING SITE, designated SEQ ID:11451, to the nucleotide sequence of VGAM425 RNA, herein designated VGAM RNA, also designated SEQ ID:3136.

[20241] Another function of VGAM425 is therefore inhibition of Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010), a gene which functions as a cell surface protein and belongs to the immunoglobulin superfamily. Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRCAM. The function of NRCAM and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM268. Protein Tyrosine Phosphatase, Non-receptor Type 18 (brain-derived) (PTPN18, Accession NM\_014369) is another VGAM425 host target gene. PTPN18 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTPN18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of PTPN18 BINDING SITE, designated SEQ ID:15703, to the nucleotide sequence of VGAM425 RNA, herein designated VGAM RNA, also designated SEQ ID:3136.

[20242] Another function of VGAM425 is therefore inhibition of Protein Tyrosine Phosphatase, Non-receptor Type 18 (brain-derived) (PTPN18, Accession NM\_014369). Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPN18. KIAA1598 (Accession NM\_018330) is another VGAM425 host target gene. KIAA1598 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1598, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1598 BINDING SITE, designated SEQ ID:20329, to the nucleotide sequence of VGAM425 RNA, herein designated VGAM RNA, also designated SEQ ID:3136.

[20243] Another function of VGAM425 is therefore inhibition of KIAA1598 (Accession NM\_018330). Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1598. LOC196500 (Accession XM\_113734) is another VGAM425 host target gene. LOC196500 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196500 BINDING SITE, designated SEQ ID:42390, to the nucleotide sequence of VGAM425 RNA, herein designated VGAM RNA, also designated SEQ ID:3136.

[20244] Another function of VGAM425 is therefore inhibition of LOC196500 (Accession XM\_113734). Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196500. LOC219855 (Accession XM\_166184) is another VGAM425 host target gene. LOC219855 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219855, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219855 BINDING SITE, designated SEQ ID:43996, to the nucleotide sequence of VGAM425 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3136.

[20245] Another function of VGAM425 is therefore inhibition of LOC219855 (Accession XM\_166184). Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219855. LOC221814 (Accession XM\_168226) is another VGAM425 host target gene. LOC221814 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221814, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221814 BINDING SITE, designated SEQ ID:45092, to the nucleotide sequence of VGAM425 RNA, herein designated VGAM RNA, also designated SEQ ID:3136.

[20246] Another function of VGAM425 is therefore inhibition of LOC221814 (Accession XM\_168226). Accordingly, utilities of VGAM425 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221814. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 426 (VGAM426) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20247] VGAM426 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM426 was detected is described hereinabove with reference to Figs. 1–8.

[20248] VGAM426 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabies Virus. VGAM426 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20249] VGAM426 gene encodes a VGAM426 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM426 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM426 precursor RNA is designated SEQ ID:412, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:412 is located at position 5774 relative to the genome of Rabies Virus.

[20250] VGAM426 precursor RNA folds onto itself, forming VGAM426 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[20251] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM426 folded precursor RNA into VGAM426 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 46%) nucleotide se-  
quence of VGAM426 RNA is designated SEQ ID:3137, and  
is provided hereinbelow with reference to the sequence  
listing part.

[20252] VGAM426 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM426 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM426 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20253] VGAM426 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM426 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM426 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM426 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM426 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20254] The complementary binding of VGAM426 RNA, herein designated VGAM RNA, to host target binding sites on VGAM426 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM426 host target RNA into VGAM426 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20255] It is appreciated that VGAM426 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM426 host target genes. The mRNA of each one of this plurality of VGAM426 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM426 RNA, herein designated VGAM RNA, and which when bound by VGAM426 RNA causes inhibition of translation of respective one or more VGAM426 host target proteins.

[20256] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by



VGAM426 gene, herein designated VGAM GENE, on one or more VGAM426 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20257] It is yet further appreciated that a function of VGAM426 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of viral infection by Rabies Virus. Specific functions, and accordingly utilities, of VGAM426 correlate with, and may be deduced from, the identity of the host target genes which VGAM426 binds and inhibits, and the function of these host target genes, as elaborated herein—

below.

- [20258] Nucleotide sequences of the VGAM426 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM426 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM426 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM426 are further described hereinbelow with reference to Table 1.
- [20259] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM426 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM426 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [20260] As mentioned hereinabove with reference to Fig. 1, a function of VGAM426 gene, herein designated VGAM is inhibition of expression of VGAM426 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM426 correlate with, and may be deduced from, the identity of the target genes which VGAM426 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20261] Calsequestrin 2 (cardiac muscle) (CASQ2, Accession NM\_001232) is a VGAM426 host target gene. CASQ2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CASQ2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CASQ2 BINDING SITE, designated SEQ ID:6904, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20262] A function of VGAM426 is therefore inhibition of Calsequestrin 2 (cardiac muscle) (CASQ2, Accession NM\_001232). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CASQ2. NIMA (never in mitosis gene a)-related Kinase 6 (NEK6, Accession NM\_014397) is another VGAM426 host target gene. NEK6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEK6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEK6 BINDING SITE, designated SEQ ID:15740, to the nu-

cleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20263] Another function of VGAM426 is therefore inhibition of NIMA (never in mitosis gene a)-related Kinase 6 (NEK6, Accession NM\_014397), a gene which regulates nuclear and cytoplasmic aspects of the mitotic cycle. Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEK6. The function of NEK6 has been established by previous studies. The *Aspergillus nidulans* 'never in mitosis A' (NIMA) gene encodes a serine/threonine kinase that controls initiation of mitosis. NIMA-related kinases (NEKs) are a group of protein kinases that are homologous to NIMA. Evidence suggests that NEKs perform functions similar to those of NIMA. Li et al. (1999) reported the cloning of a human liver cDNA encoding NEK6. Kimura and Okano (2001) determined that NEK6 and NEK7 (OMIM Ref. No. 606848) share 77% amino acid identity. By Northern blot analysis, Li et al. (1999) detected 1.6-, 2.6-, and 9.5-kb NEK6 transcripts. The 1.6-kb transcript was expressed at highest levels in liver and placenta. By RT-PCR, Kimura and Okano (2001) found expression of NEK6 in all tissues examined.

[20264] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20265] Kimura, M.; Okano, Y. : Identification and assignment of the human NIMA-related protein kinase 7 gene (NEK7) to human chromosome 1q31.3. Cytogenet. Cell Genet. 94: 33-38, 2001. ; and

[20266] Li, M. Z.; Yu, L.; Liu, Q.; Chu, J. Y.; Zhao, S. Y. : Assignment of NEK6, a NIMA-related gene, to human chromosome 9q33.3-q34.11 by radiation hybrid mapping. Cytogenet. Cell Genet. 87:.

[20267] Further studies establishing the function and utilities of NEK6 are found in John Hopkins OMIM database record ID 604884, and in cited publications numbered 6947-6948 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Kinase, CGMP-dependent, Type II (PRKG2, Accession NM\_006259) is another VGAM426 host target gene. PRKG2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKG2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

PRKG2 BINDING SITE, designated SEQ ID:12942, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20268] Another function of VGAM426 is therefore inhibition of Protein Kinase, CGMP-dependent, Type II (PRKG2, Accession NM\_006259), a gene which regulate a great variety of functions, including smooth muscle relaxation, neuronal excitability, and epithelial electrolyte transport. Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKG2. The function of PRKG2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM16. Winged-helix Nude (WHN, Accession NM\_003593) is another VGAM426 host target gene. WHN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WHN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WHN BINDING SITE, designated SEQ ID:9648, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20269] Another function of VGAM426 is therefore inhibition of Winged-helix Nude (WHN, Accession NM\_003593), a gene which plays a role in transcriptional regulation. Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WHN. The function of WHN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM403. Allantoicase (ALLC, Accession NM\_018436) is another VGAM426 host target gene. ALLC BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ALLC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALLC BINDING SITE, designated SEQ ID:20497, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20270] Another function of VGAM426 is therefore inhibition of Allantoicase (ALLC, Accession NM\_018436). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALLC. E74-like Factor 1 (ets domain transcription

factor) (ELF1, Accession XM\_049376) is another VGAM426 host target gene. ELF1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ELF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELF1 BINDING SITE, designated SEQ ID:35402, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20271] Another function of VGAM426 is therefore inhibition of E74-like Factor 1 (ets domain transcription factor) (ELF1, Accession XM\_049376). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELF1. Epsin 3 (EPN3, Accession NM\_017957) is another VGAM426 host target gene. EPN3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by EPN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPN3 BINDING SITE, designated SEQ ID:19668, to the nucleotide sequence of VGAM426 RNA,



herein designated VGAM RNA, also designated SEQ ID:3137.

[20272] Another function of VGAM426 is therefore inhibition of Epsin 3 (EPN3, Accession NM\_017957). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPN3. FLJ11806 (Accession NM\_024824) is another VGAM426 host target gene. FLJ11806 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ11806, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11806 BINDING SITE, designated SEQ ID:24216, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20273] Another function of VGAM426 is therefore inhibition of FLJ11806 (Accession NM\_024824). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11806. FLJ20294 (Accession NM\_017749) is another VGAM426 host target gene. FLJ20294 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA

encoded by FLJ20294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20294 BINDING SITE, designated SEQ ID:19343, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20274] Another function of VGAM426 is therefore inhibition of FLJ20294 (Accession NM\_017749). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20294. FLJ23462 (Accession NM\_024843) is another VGAM426 host target gene. FLJ23462 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23462, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23462 BINDING SITE, designated SEQ ID:24264, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20275] Another function of VGAM426 is therefore inhibition of FLJ23462 (Accession NM\_024843). Accordingly, utilities of

VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23462. KIAA1202 (Accession XM\_050478) is another VGAM426 host target gene. KIAA1202 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1202, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1202 BINDING SITE, designated SEQ ID:35639, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20276] Another function of VGAM426 is therefore inhibition of KIAA1202 (Accession XM\_050478). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1202. MGC2452 (Accession NM\_032644) is another VGAM426 host target gene. MGC2452 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC2452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2452

BINDING SITE, designated SEQ ID:26374, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20277] Another function of VGAM426 is therefore inhibition of MGC2452 (Accession NM\_032644). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2452. P115 (Accession NM\_003715) is another VGAM426 host target gene. P115 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P115, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P115 BINDING SITE, designated SEQ ID:9812, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20278] Another function of VGAM426 is therefore inhibition of P115 (Accession NM\_003715). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P115. Signal Sequence Receptor, Alpha (translocon-associated protein alpha) (SSR1, Accession NM\_003144) is another

VGAM426 host target gene. SSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSR1 BINDING SITE, designated SEQ ID:9115, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20279] Another function of VGAM426 is therefore inhibition of Signal Sequence Receptor, Alpha (translocon-associated protein alpha) (SSR1, Accession NM\_003144). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSR1. Testis Specific, 14 (TSGA14, Accession NM\_018718) is another VGAM426 host target gene. TSGA14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSGA14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSGA14 BINDING SITE, designated SEQ ID:20795, to the nucleotide sequence of VGAM426 RNA,

herein designated VGAM RNA, also designated SEQ ID:3137.

[20280] Another function of VGAM426 is therefore inhibition of Testis Specific, 14 (TSGA14, Accession NM\_018718). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSGA14. LOC146337 (Accession XM\_096982) is another VGAM426 host target gene. LOC146337 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146337 BINDING SITE, designated SEQ ID:40692, to the nucleotide sequence of VGAM426 RNA, herein designated VGAM RNA, also designated SEQ ID:3137.

[20281] Another function of VGAM426 is therefore inhibition of LOC146337 (Accession XM\_096982). Accordingly, utilities of VGAM426 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146337. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 427 (VGAM427) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20282] VGAM427 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM427 was detected is described hereinabove with reference to Figs. 1–8.

[20283] VGAM427 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabies Virus. VGAM427 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20284] VGAM427 gene encodes a VGAM427 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM427 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM427 precursor RNA is designated SEQ ID:413, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:413 is located at position 5539 relative to the genome of Rabies Virus.

[20285] VGAM427 precursor RNA folds onto itself, forming VGAM427 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20286] An enzyme complex designated DICER COMPLEX, `dices` the VGAM427 folded precursor RNA into VGAM427 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM427 RNA is designated SEQ ID:3138, and is provided hereinbelow with reference to the sequence listing part.

[20287] VGAM427 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM427 host target RNA, herein designated VGAM



HOST TARGET RNA. VGAM427 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20288] VGAM427 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM427 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM427 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM427 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM427 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[20289] The complementary binding of VGAM427 RNA, herein designated VGAM RNA, to host target binding sites on VGAM427 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM427 host target RNA into VGAM427 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20290] It is appreciated that VGAM427 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM427 host target genes. The mRNA of each one of this plurality of VGAM427 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM427 RNA, herein designated VGAM RNA, and which when bound by VGAM427 RNA causes inhibition of translation of respective one or more VGAM427 host target proteins.

[20291] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM427 gene, herein designated VGAM GENE, on one or more VGAM427 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20292] It is yet further appreciated that a function of VGAM427 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of viral infection by Rabies Virus. Specific functions, and accordingly utilities, of VGAM427 correlate with, and may be deduced from, the identity of the host

target genes which VGAM427 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20293] Nucleotide sequences of the VGAM427 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM427 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM427 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM427 are further described hereinbelow with reference to Table 1.

[20294] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM427 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM427 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20295] As mentioned hereinabove with reference to Fig. 1, a function of VGAM427 gene, herein designated VGAM is inhibition of expression of VGAM427 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM427 correlate with, and may be deduced from, the identity of the target genes which VGAM427

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20296] Aldehyde Dehydrogenase 3 Family, Member A2

(ALDH3A2, Accession XM\_045060) is a VGAM427 host target gene. ALDH3A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALDH3A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALDH3A2 BINDING SITE, designated SEQ ID:34339, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20297] A function of VGAM427 is therefore inhibition of Aldehyde Dehydrogenase 3 Family, Member A2 (ALDH3A2, Accession XM\_045060). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALDH3A2. Calnexin (CANX, Accession XM\_113469) is another VGAM427 host target gene. CANX BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CANX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of CANX BINDING SITE, designated SEQ ID:42275, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20298] Another function of VGAM427 is therefore inhibition of Calnexin (CANX, Accession XM\_113469), a gene which may function as a chaperone in the endoplasmic reticulum, involved in the secretion of proteins from the ER to the outer cellular membrane. Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CANX. The function of CANX and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM116. Integrin, Beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) (ITGB1, Accession NM\_002211) is another VGAM427 host target gene. ITGB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of ITGB1 BINDING SITE, designated SEQ ID:7976, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20299] Another function of VGAM427 is therefore inhibition of Integrin, Beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12) (ITGB1, Accession NM\_002211), a gene which acts as a fibronectin receptor. Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGB1. The function of ITGB1 has been established by previous studies. See 135620. The fibronectin receptors contain a beta subunit that appears to be analogous to band 3 of integrin (Pytela et al., 1986; Johansson et al., 1987). Hynes (1987) proposed that there are 3 subfamilies within the family of human adhesion protein receptor heterodimers based upon the number of different beta subunits. The other 2 subfamilies are the platelet and the endothelial cell heterodimers, which use GP IIIa (OMIM Ref. No. 173470), and the leukocyte heterodimers, which contain a 95,000 Da beta subunit that is homologous to GP IIIa but is clearly a different protein (OMIM Ref. No. 116920). Zhang et al. (1988) examined human-mouse hybrid cells by indirect immunofluores-

cence with a monoclonal antibody that recognizes the beta subunit of the human fibronectin receptor. Cells that expressed the antigen at their surface were sorted by FACS and karyotyped. The findings, strengthened by isozyme analysis of markers for chromosomes 9 and 10, suggested that the beta subunit is located on 10p. By examining the cation dependence of JAM2 (OMIM Ref. No. 606870) adhesion to a T-cell line, Cunningham et al. (2002) identified a manganese-enhanced binding component indicative of integrin involvement. Using neutralizing integrin antibodies, they showed that the manganese-enhanced binding component was due to an interaction between JAM2 and ITGA4/ITGB1. However, the interaction was only enabled following prior adhesion of JAM2 to JAM3 (OMIM Ref. No. 606871). Cunningham et al. (2002) determined that the engagement of all these ligands occurs through a nonacidic residue in an Ig-like fold of JAM2. An inhibitor of ITGA4, TBC772, attenuated the manganese-enhanced binding. Animal model experiments lend further support to the function of ITGB1. Graus-Porta et al. (2001) used Cre/Lox-mediated recombination to generate mice with an *Itgb1*-null allele in the precursors of neurons and glia, thereby inactivating all beta-1-class



integrin receptors in the nervous system. The mice died prematurely after birth with severe brain malformations. Using histologic sections of brains at varying ages, Graus-Porta et al. (2001) observed that cortical hemispheres and cerebellar folia fuse, and cortical laminae are perturbed in the knockout mice. These defects result from disorganization of the cortical marginal zone, where Graus-Porta et al. (2001) hypothesized that beta-1-class integrins regulate glial endfeet anchorage, meningeal basement membrane remodeling, and formation of the Cajal-Retzius cell layer. Graus-Porta et al. (2001) concluded that beta-1-class integrins are not essential for neuron-glia interactions and neuronal migration during corticogenesis. They noted that the phenotype of the beta-1-deficient mice resembles pathologic changes observed in human cortical dysplasias, suggesting that defective integrin-mediated signal transduction contributes to the development of some of these diseases

[20300] It is appreciated that the abovementioned animal model for ITGB1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20301] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [20302] Zhang, Y.; Saison, M.; Spaepen, M.; De Strooper, B.; Van Leuven, F.; David, G.; Van den Berghe, H.; Cassiman, J.-J. : Mapping of human fibronectin receptor beta subunit gene to chromosome 10. *Somat. Cell Molec. Genet.* 14: 99–104, 1988. ; and
- [20303] Graus–Porta, D.; Blaess, S.; Senften, M.; Littlewood–Evans, A.; Damsky, C.; Huang, Z.; Orban, P.; Klein, R.; Schittny, J. C.; Muller, U. : Beta–1–class integrins regulate the development.
- [20304] Further studies establishing the function and utilities of ITGB1 are found in John Hopkins OMIM database record ID 135630, and in cited publications numbered 3340–335 and 3463 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphatidylinositol–4–phosphate 5–kinase, Type I, Alpha (PIP5K1A, Accession NM\_003557) is another VGAM427 host target gene. PIP5K1A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PIP5K1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com–

plementarity of the nucleotide sequences of PIP5K1A BINDING SITE, designated SEQ ID:9601, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20305] Another function of VGAM427 is therefore inhibition of Phosphatidylinositol-4-phosphate 5-kinase, Type I, Alpha (PIP5K1A, Accession NM\_003557), a gene which is responsible for the synthesis of PtdIns(4,5)P<sub>2</sub>. Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP5K1A. The function of PIP5K1A has been established by previous studies. By searching sequence databases with peptide sequences obtained from the 68-kD type I PIP5K purified from bovine erythrocytes, Loijens and Anderson (1996) identified a human EST encoding PIP5K1A, which they called PIP5KI-alpha. They screened a human fetal brain cDNA library and isolated full-length PIP5K1A cDNAs. The deduced 549-amino acid protein has the conserved kinase homology domain of PIP5K family members. Within this domain, PIP5K1A shows 83% and 35% amino acid identity with PIP5K1B (OMIM Ref. No. 602745) and PIP5K2A (OMIM Ref. No. 603140), respectively. Overall, the PIP5K1A and PIP5K1B proteins are

64% identical. Recombinant PIP5K1A expressed in bacteria had a molecular mass of approximately 66.3 kD by Western blot analysis. The authors isolated additional PIP5K1A cDNAs which they suggested represent splicing isoforms. Northern blot analysis detected a major 4.2-kb PIP5K1A transcript which had a wide tissue distribution. Using deletion mutant analysis, Ishihara et al. (1998) identified an approximately 380-amino acid minimal core sequence of mouse Pip5k1a that was sufficient for phosphatidylinositol 4-phosphate kinase activity. Overexpression of mouse Pip5k1a in COS7 cells induced an increase in short actin fibers and a decrease in actin stress fibers.

[20306] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20307] Loijens, J. C.; Anderson, R. A. : Type I phosphatidylinositol-4-phosphate 5-kinases are distinct members of this novel lipid kinase family. *J. Biol. Chem.* 271: 32937-32943, 1996. ; and

[20308] Xie, Y.; Zhu, L.; Zhao, G. : Assignment of type I phosphatidylinositol-4-phosphate 5-kinase (PIP5K1A) to human chromosome bands 1q22-q24 by in situ hybridization. *Cytogenet. Cell Genet.*

[20309] Further studies establishing the function and utilities of PIP5K1A are found in John Hopkins OMIM database record ID 603275, and in cited publications numbered 8741–5068 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Usher Syndrome 3A (USH3A, Accession NM\_052995) is another VGAM427 host target gene. USH3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by USH3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USH3A BINDING SITE, designated SEQ ID:27559, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20310] Another function of VGAM427 is therefore inhibition of Usher Syndrome 3A (USH3A, Accession NM\_052995). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USH3A. Zinc Finger Protein 189 (ZNF189, Accession NM\_003452) is another VGAM427 host target gene. ZNF189 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

ZNF189, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF189 BINDING SITE, designated SEQ ID:9503, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20311] Another function of VGAM427 is therefore inhibition of Zinc Finger Protein 189 (ZNF189, Accession NM\_003452). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF189. FLJ10546 (Accession XM\_002989) is another VGAM427 host target gene. FLJ10546 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10546, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10546 BINDING SITE, designated SEQ ID:29911, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20312] Another function of VGAM427 is therefore inhibition of

FLJ10546 (Accession XM\_002989). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10546. FLJ23563 (Accession XM\_041701) is another VGAM427 host target gene. FLJ23563 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23563, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23563 BINDING SITE, designated SEQ ID:33558, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20313] Another function of VGAM427 is therefore inhibition of FLJ23563 (Accession XM\_041701). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23563. LOC115294 (Accession XM\_054302) is another VGAM427 host target gene. LOC115294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of LOC115294 BINDING SITE, designated SEQ ID:36142, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20314] Another function of VGAM427 is therefore inhibition of LOC115294 (Accession XM\_054302). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115294. LOC150606 (Accession XM\_097928) is another VGAM427 host target gene. LOC150606 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150606, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150606 BINDING SITE, designated SEQ ID:41233, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20315] Another function of VGAM427 is therefore inhibition of LOC150606 (Accession XM\_097928). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150606. LOC206426 (Accession XM\_116505) is an-



other VGAM427 host target gene. LOC206426 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC206426, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC206426 BINDING SITE, designated SEQ ID:43113, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20316] Another function of VGAM427 is therefore inhibition of LOC206426 (Accession XM\_116505). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC206426. LOC55901 (Accession NM\_018676) is another VGAM427 host target gene. LOC55901 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC55901, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC55901 BINDING SITE, designated SEQ ID:20749, to the nucleotide sequence of VGAM427 RNA, herein designated VGAM RNA, also designated SEQ ID:3138.

[20317] Another function of VGAM427 is therefore inhibition of LOC55901 (Accession NM\_018676). Accordingly, utilities of VGAM427 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC55901. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 428 (VGAM428) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20318] VGAM428 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM428 was detected is described hereinabove with reference to Figs. 1–8.

[20319] VGAM428 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabies Virus. VGAM428 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20320] VGAM428 gene encodes a VGAM428 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM428 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM428 precursor RNA is designated SEQ ID:414, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:414 is located at position 6617 relative to the genome of Rabies Virus.

[20321] VGAM428 precursor RNA folds onto itself, forming VGAM428 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20322] An enzyme complex designated DICER COMPLEX, `dices` the VGAM428 folded precursor RNA into VGAM428 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 58%) nucleotide se-

quence of VGAM428 RNA is designated SEQ ID:3139, and is provided hereinbelow with reference to the sequence listing part.

[20323] VGAM428 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM428 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM428 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[20324] VGAM428 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM428 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM428 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM428 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM428 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[20325] The complementary binding of VGAM428 RNA, herein designated VGAM RNA, to host target binding sites on VGAM428 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM428 host target RNA into VGAM428 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20326] It is appreciated that VGAM428 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM428 host target genes. The mRNA of each one of this plurality of VGAM428 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM428 RNA, herein designated VGAM RNA, and which when bound by VGAM428 RNA causes inhibition of translation of respective one or more VGAM428 host target proteins.

[20327] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM428 gene, herein designated VGAM GENE, on one or more VGAM428 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20328] It is yet further appreciated that a function of VGAM428 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of viral infection by Rabies Virus. Specific functions, and accordingly utilities, of VGAM428 correlate with, and may be deduced from, the identity of the host target genes which VGAM428 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20329] Nucleotide sequences of the VGAM428 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM428 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM428 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM428 are further described hereinbelow with reference to Table 1.

[20330] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM428 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM428 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20331] As mentioned hereinabove with reference to Fig. 1, a function of VGAM428 gene, herein designated VGAM is inhibition of expression of VGAM428 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM428 correlate with, and may be deduced from, the identity of the target genes which VGAM428 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20332] Paired Mesoderm Homeo Box 1 (PMX1, Accession NM\_006902) is a VGAM428 host target gene. PMX1 BINDING SITE1 and PMX1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PMX1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PMX1 BINDING SITE1 and PMX1 BINDING SITE2, designated SEQ ID:13782 and SEQ ID:22917 respectively, to the nucleotide sequence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20333] A function of VGAM428 is therefore inhibition of Paired Mesoderm Homeo Box 1 (PMX1, Accession NM\_006902), a gene which acts as a transcriptional regulator of muscle



creatine kinase. Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PMX1. The function of PMX1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM381. DIS3 (Accession NM\_014953) is another VGAM428 host target gene. DIS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DIS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DIS3 BINDING SITE, designated SEQ ID:17299, to the nucleotide sequence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20334] Another function of VGAM428 is therefore inhibition of DIS3 (Accession NM\_014953). Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIS3. FLJ22329 (Accession NM\_024656) is another VGAM428 host target gene. FLJ22329 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22329, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22329 BINDING SITE, designated SEQ ID:23957, to the nucleotide sequence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20335] Another function of VGAM428 is therefore inhibition of FLJ22329 (Accession NM\_024656). Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22329. LEC3 (Accession NM\_015236) is another VGAM428 host target gene. LEC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LEC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LEC3 BINDING SITE, designated SEQ ID:17571, to the nucleotide sequence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20336] Another function of VGAM428 is therefore inhibition of LEC3 (Accession NM\_015236). Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with LEC3.

SP192 (Accession NM\_021639) is another VGAM428 host target gene. SP192 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SP192, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SP192 BINDING SITE, designated SEQ ID:22298, to the nucleotide sequence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20337] Another function of VGAM428 is therefore inhibition of SP192 (Accession NM\_021639). Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SP192. LOC144667 (Accession XM\_096648) is another VGAM428 host target gene. LOC144667 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC144667, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144667 BINDING SITE, designated SEQ ID:40451, to the nucleotide se-

quence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20338] Another function of VGAM428 is therefore inhibition of LOC144667 (Accession XM\_096648). Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144667. LOC151996 (Accession XM\_098151) is another VGAM428 host target gene. LOC151996 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151996, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151996 BINDING SITE, designated SEQ ID:41416, to the nucleotide sequence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20339] Another function of VGAM428 is therefore inhibition of LOC151996 (Accession XM\_098151). Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151996. LOC256113 (Accession XM\_172989) is another VGAM428 host target gene. LOC256113 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC256113, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256113 BINDING SITE, designated SEQ ID:46260, to the nucleotide sequence of VGAM428 RNA, herein designated VGAM RNA, also designated SEQ ID:3139.

[20340] Another function of VGAM428 is therefore inhibition of LOC256113 (Accession XM\_172989). Accordingly, utilities of VGAM428 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256113. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 429 (VGAM429) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20341] VGAM429 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM429 was detected is described hereinabove with reference to Figs. 1–8.

[20342] VGAM429 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Rabbit Hemorrhagic Disease Virus. VGAM429 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20343] VGAM429 gene encodes a VGAM429 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM429 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM429 precursor RNA is designated SEQ ID:415, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:415 is located at position 4010 relative to the genome of Rabbit Hemorrhagic Disease Virus.

[20344] VGAM429 precursor RNA folds onto itself, forming VGAM429 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20345] An enzyme complex designated DICER COMPLEX, `dices` the VGAM429 folded precursor RNA into VGAM429 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM429 RNA is designated SEQ ID:3140, and is provided hereinbelow with reference to the sequence listing part.

[20346] VGAM429 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM429 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM429 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20347] VGAM429 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM429 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM429 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM429 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM429 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20348] The complementary binding of VGAM429 RNA, herein designated VGAM RNA, to host target binding sites on VGAM429 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM429 host tar-



get RNA into VGAM429 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20349] It is appreciated that VGAM429 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM429 host target genes. The mRNA of each one of this plurality of VGAM429 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM429 RNA, herein designated VGAM RNA, and which when bound by VGAM429 RNA causes inhibition of translation of respective one or more VGAM429 host target proteins.

[20350] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM429 gene, herein designated VGAM GENE, on one or more VGAM429 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20351] It is yet further appreciated that a function of VGAM429 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of viral infection by Rabbit Hemorrhagic Disease Virus. Specific functions, and accordingly utilities, of VGAM429 correlate with, and may be deduced from, the identity of the host target genes which VGAM429 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20352] Nucleotide sequences of the VGAM429 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM429 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM429 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM429 are further

described hereinbelow with reference to Table 1.

[20353] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM429 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM429 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20354] As mentioned hereinabove with reference to Fig. 1, a function of VGAM429 gene, herein designated VGAM is inhibition of expression of VGAM429 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM429 correlate with, and may be deduced from, the identity of the target genes which VGAM429 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20355] Angiopoietin 1 (ANGPT1, Accession NM\_001146) is a VGAM429 host target gene. ANGPT1 BINDING SITE1 and ANGPT1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ANGPT1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of ANGPT1 BINDING SITE1 and ANGPT1 BINDING SITE2, designated SEQ ID:6815 and SEQ ID:29290 respectively, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20356] A function of VGAM429 is therefore inhibition of Angiopoietin 1 (ANGPT1, Accession NM\_001146), a gene which binds and activates tie2 receptor by inducing its tyrosine phosphorylation. Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANGPT1. The function of ANGPT1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM291. Retinoblastoma Binding Protein 9 (RBBP9, Accession XM\_046553) is another VGAM429 host target gene. RBBP9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RBBP9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RBBP9 BINDING SITE, designated SEQ ID:34743, to the nucleotide sequence of VGAM429 RNA,

herein designated VGAM RNA, also designated SEQ ID:3140.

[20357] Another function of VGAM429 is therefore inhibition of Retinoblastoma Binding Protein 9 (RBBP9, Accession XM\_046553). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RBBP9. Ubiquitin Specific Protease 11 (USP11, Accession NM\_004651) is another VGAM429 host target gene. USP11 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by USP11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USP11 BINDING SITE, designated SEQ ID:11021, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20358] Another function of VGAM429 is therefore inhibition of Ubiquitin Specific Protease 11 (USP11, Accession NM\_004651), a gene which removes ubiquitin from ubiquitin-conjugated proteins. Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USP11.

The function of USP11 has been established by previous studies. Swanson et al. (1996) used a differential hybridization screen to isolate a novel cDNA from a human retina library. The cDNA encodes a protein of 690 amino acids and has strong homology to the proteins encoded by a variety of ubiquitin hydrolases (p values ranging between  $2.4e-265$  and  $1.4e-13$ ). Swanson et al. (1996) reviewed the role of ubiquitination in protein degradation and presented evidence that disturbances in protein processing and turnover can lead to retinal degeneration. They noted that there are at least 4 X-linked retinal diseases that map to a region within or overlapping the UHX1 interval. They cited evidence indicating that ubiquitin hydrolases play a role in oncogenesis (oncogenes and tumor suppressor gene products are degraded in ubiquitin-dependent pathways) and that the region of loss of heterozygosity in ovarian cancer lies within the mapping interval defined for UHX1. Swanson et al. (1996) mapped the structural gene encoding this cDNA, which they designated UHX1, to Xp21.2-p11.2 by somatic cell hybridization. Stoddart et al. (1999) mapped the UHX1 gene to Xp11.3 by inclusion within a YAC contig

[20359] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

[20360] Swanson, D. A.; Freund, C. L.; Ploder, L.; McInnes, R. R.; Valle, D. : A ubiquitin C-terminal hydrolase gene on the proximal short arm of the X chromosome: implications for X-linked retinal disorders. Hum. Molec. Genet. 5:

533-538, 1996. ; and

[20361] Stoddart, K. L.; Jermak, C.; Nagaraja, R.; Schlessinger, D.; Bech-Hansen, N. T. : Physical map covering a 2 Mb region in human Xp11.3 distal to DX6849. Gene 227: 111-116, 1999.

[20362] Further studies establishing the function and utilities of USP11 are found in John Hopkins OMIM database record ID 300050, and in cited publications numbered 8997-8998 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZP564O0463 (Accession NM\_014156) is another VGAM429 host target gene. DKFZP564O0463 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564O0463, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of DKFZP564O0463 BINDING SITE, designated SEQ ID:15444, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20363] Another function of VGAM429 is therefore inhibition of DKFZP564O0463 (Accession NM\_014156). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564O0463. E74-like Factor 4 (ets domain transcription factor) (ELF4, Accession NM\_001421) is another VGAM429 host target gene. ELF4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ELF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELF4 BINDING SITE, designated SEQ ID:7125, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20364] Another function of VGAM429 is therefore inhibition of E74-like Factor 4 (ets domain transcription factor) (ELF4, Accession NM\_001421). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases



and clinical conditions associated with ELF4. FLJ20716 (Accession NM\_017938) is another VGAM429 host target gene. FLJ20716 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20716, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20716 BINDING SITE, designated SEQ ID:19632, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20365] Another function of VGAM429 is therefore inhibition of FLJ20716 (Accession NM\_017938). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20716. HCC-4 (Accession NM\_138611) is another VGAM429 host target gene. HCC-4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HCC-4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCC-4 BINDING SITE, designated SEQ ID:28898, to the nucleotide sequence of VGAM429

RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20366] Another function of VGAM429 is therefore inhibition of HCC-4 (Accession NM\_138611). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCC-4. IKKE (Accession NM\_014002) is another VGAM429 host target gene. IKKE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IKKE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IKKE BINDING SITE, designated SEQ ID:15205, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20367] Another function of VGAM429 is therefore inhibition of IKKE (Accession NM\_014002). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IKKE. KIAA0794 (Accession XM\_087353) is another VGAM429 host target gene. KIAA0794 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by KIAA0794, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0794 BINDING SITE, designated SEQ ID:39183, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20368] Another function of VGAM429 is therefore inhibition of KIAA0794 (Accession XM\_087353). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0794. KIAA1522 (Accession XM\_036299) is another VGAM429 host target gene. KIAA1522 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1522, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1522 BINDING SITE, designated SEQ ID:32420, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20369] Another function of VGAM429 is therefore inhibition of KIAA1522 (Accession XM\_036299). Accordingly, utilities

of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1522. LOC146315 (Accession XM\_027576) is another VGAM429 host target gene. LOC146315 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC146315, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146315 BINDING SITE, designated SEQ ID:30534, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20370] Another function of VGAM429 is therefore inhibition of LOC146315 (Accession XM\_027576). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146315. LOC146515 (Accession XM\_085493) is another VGAM429 host target gene. LOC146515 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC146515, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC146515 BINDING SITE, designated SEQ ID:38195, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20371] Another function of VGAM429 is therefore inhibition of LOC146515 (Accession XM\_085493). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146515. LOC221025 (Accession XM\_167644) is another VGAM429 host target gene. LOC221025 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221025, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221025 BINDING SITE, designated SEQ ID:44746, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20372] Another function of VGAM429 is therefore inhibition of LOC221025 (Accession XM\_167644). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221025. LOC92661 (Accession XM\_046465) is another VGAM429 host target gene. LOC92661 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92661, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92661 BINDING SITE, designated SEQ ID:34726, to the nucleotide sequence of VGAM429 RNA, herein designated VGAM RNA, also designated SEQ ID:3140.

[20373] Another function of VGAM429 is therefore inhibition of LOC92661 (Accession XM\_046465). Accordingly, utilities of VGAM429 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92661. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 430 (VGAM430) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20374] VGAM430 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM430 was detected is described hereinabove with reference to Figs. 1-8.

[20375] VGAM430 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabbit Hemorrhagic Disease Virus. VGAM430 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20376] VGAM430 gene encodes a VGAM430 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM430 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM430 precursor RNA is designated SEQ ID:416, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:416 is located at position 6133 relative to the genome of Rabbit Hemorrhagic Disease Virus.

[20377] VGAM430 precursor RNA folds onto itself, forming VGAM430 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[20378] An enzyme complex designated DICER COMPLEX, `dices` the VGAM430 folded precursor RNA into VGAM430 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM430 RNA is designated SEQ ID:3141, and is provided hereinbelow with reference to the sequence listing part.

[20379] VGAM430 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM430 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM430 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20380] VGAM430 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM430 host target



RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM430 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM430 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM430 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20381] The complementary binding of VGAM430 RNA, herein designated VGAM RNA, to host target binding sites on VGAM430 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM430 host target RNA into VGAM430 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20382] It is appreciated that VGAM430 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM430 host target genes. The mRNA of each one of this plurality of VGAM430 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM430 RNA, herein designated VGAM RNA, and which when bound by VGAM430 RNA causes inhibition of translation of respective one or more VGAM430 host target proteins.

[20383] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM430 gene, herein designated VGAM GENE, on one or more VGAM430 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20384] It is yet further appreciated that a function of VGAM430 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of viral infection by Rabbit Hemorrhagic Disease Virus. Specific functions, and accordingly utilities, of VGAM430 correlate with, and may be deduced from, the identity of the host target genes which VGAM430 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20385] Nucleotide sequences of the VGAM430 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM430 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM430 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM430 are further described hereinbelow with reference to Table 1.

[20386] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM430 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM430 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20387] As mentioned hereinabove with reference to Fig. 1, a function of VGAM430 gene, herein designated VGAM is inhibition of expression of VGAM430 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM430 correlate with, and may be deduced from, the identity of the target genes which VGAM430 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20388] Adenosine A3 Receptor (ADORA3, Accession NM\_000677) is a VGAM430 host target gene. ADORA3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ADORA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of ADORA3 BINDING SITE, designated SEQ ID:6333, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20389] A function of VGAM430 is therefore inhibition of Adenosine A3 Receptor (ADORA3, Accession NM\_000677), a gene which the activity of this receptor is mediated by G proteins which inhibits adenylyl cyclase. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADORA3. The function of ADORA3 has been established by previous studies. There are 3 types of adenosine receptors, each of which contains 7 transmembrane domains and interacts with G proteins. The A1 receptors inhibit adenylyl cyclase while the type A2 receptors stimulate activity. Each adenosine receptor has a specific pattern of ligand binding and a unique tissue distribution (Zhao et al., 1995). The A3 adenosine receptor was cloned from rat brain (Zhou et al., 1992) and human heart (Sajjadi and Firestein, 1993). The rat A3 receptor protein is about 50 to 60% identical to the A1 and A2 receptors and has been shown to be an inhibitor of adenylyl cyclase activity. By interspecific backcross analysis, Wilkie et al. (1993)

localized the adenosine A3 receptor to chromosome 3 in the mouse, suggesting a human chromosomal localization of 1p13 from known mouse/human linkage homologies. Zhao et al. (1995) also mapped the A3 receptor by inter-specific backcross analysis to mouse chromosome 3. This prediction was confirmed by Monitto et al. (1995), who mapped the ADORA3 gene to human 1p at a distance between 8 and 17 cM from the centromere. PCR amplification of DNAs from a human/rodent somatic cell hybrid mapping panel was followed by PCR analysis of pooled YAC DNA. From the marker content of the YAC, the gene was thought to map to 1p21-p13.

[20390] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20391] Zhao, Z.; Ravid, S.; Ravid, K. : Chromosomal mapping of the mouse A3 adenosine receptor gene, Adora3. Genomics 30: 118-119, 1995. ; and

[20392] Monitto, C. L.; Levitt, R. C.; DiSilvestre, D.; Holroyd, K. J. : Localization of the A(3) adenosine receptor gene (ADORA3) to human chromosome 1p. Genomics 26: 637-638, 1995.

[20393] Further studies establishing the function and utilities of

ADORA3 are found in John Hopkins OMIM database record ID 600445, and in cited publications numbered 10222–1022 and 11892–10226 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. BCL2–antagonist/killer 1 (BAK1, Accession XM\_166333) is another VGAM430 host target gene. BAK1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by BAK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BAK1 BINDING SITE, designated SEQ ID:44176, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20394] Another function of VGAM430 is therefore inhibition of BCL2–antagonist/killer 1 (BAK1, Accession XM\_166333), a gene which accelerates programmed cell death by binding to, and antagonizing the a repressor bcl–2. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BAK1. The function of BAK1 has been established by previous studies. The BCL2 oncogene (OMIM Ref. No. 151430), which is activated in follicular lymphomas, func–

tions as a potent suppressor of apoptosis under diverse conditions. Chittenden et al. (1995) and Kiefer et al. (1995) described the cDNA cloning and functional analysis of a new BCL2 homolog, BAK, which promotes cell death and counteracts the protection from apoptosis provided by BCL2. Moreover, Chittenden et al. (1995) found that enforced expression of BAK induced rapid and extensive apoptosis of serum-deprived fibroblasts. This suggested that BAK may be directly involved in activating the cell death machinery. Kiefer et al. (1995) pointed out that, like BAX (OMIM Ref. No. 600040), the BAK gene product primarily enhances apoptotic cell death following an appropriate stimulus. Unlike BAX, however, BAK can inhibit cell death in an Epstein-Barr virus-transformed cell line. The caspase-activated form of BID (OMIM Ref. No. 601997), tBID, triggers the homooligomerization of multidomain conserved proapoptotic family members BAK or BAX, resulting in the release of cytochrome c from mitochondria. Wei et al. (2001) found that cells lacking both BAK and BAX, but not cells lacking only one of these components, are completely resistant to tBID-induced cytochrome c release and apoptosis. Moreover, doubly deficient cells are resistant to multiple apoptotic stimuli that act through



disruption of mitochondrial function: staurosporine, ultraviolet radiation, growth factor deprivation, etoposide, and the endoplasmic reticulum stress stimuli thapsigargin and tunicamycin. Thus, Wei et al. (2001) concluded that activation of a 'multidomain' proapoptotic member, BAK or BAX, appears to be an essential gateway to mitochondrial dysfunction required for cell death in response to diverse stimuli. Animal model experiments lend further support to the function of BAK1. Proapoptotic Bcl2 family members have been proposed to play a central role in regulating apoptosis, yet mice lacking Bax display limited phenotypic abnormalities. Lindsten et al. (2000) found that Bak  $-/-$  mice were developmentally normal and reproductively fit and failed to develop any age-related disorders. However, when Bak-deficient mice were mated to Bax-deficient mice to create mice lacking both genes, the majority of Bax  $-/-$  Bak  $-/-$  animals died perinatally, with fewer than 10% surviving into adulthood. Bax  $-/-$  Bak  $-/-$  mice displayed multiple developmental defects, including persistence of interdigital webs, an imperforate vaginal canal, and accumulation of excess cells within both the central nervous and hematopoietic systems. Thus, the authors concluded that Bax and Bak have overlapping roles in the

regulation of apoptosis during mammalian development and tissue homeostasis.

[20395] It is appreciated that the abovementioned animal model for BAK1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[20396] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20397] Chittenden, T.; Harrington, E. A.; O'Connor, R.; Fleming-ton, C.; Lutz, R. J.; Evan, G. I.; Guild, B. C. : Induction of apoptosis by the Bcl-2 homologue Bak. Nature 374: 733-736, 1995. ; and

[20398] Lindsten, T.; Ross, A. J.; King, A.; Zong, W.-X.; Rathmell, J. C.; Shiels, H. A.; Ulrich, E.; Waymire, K. G.; Mahar, P.; Frauwirth, K.; Chen, Y.; Wei, M.; and 9 others : The combined fu.

[20399] Further studies establishing the function and utilities of BAK1 are found in John Hopkins OMIM database record ID 600516, and in cited publications numbered 7163-7165, 7712, 812 and 7714 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Biglycan (BGN, Accession NM\_001711) is another VGAM430 host target gene. BGN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BGN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BGN BINDING SITE, design-

nated SEQ ID:7438, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20400] Another function of VGAM430 is therefore inhibition of Biglycan (BGN, Accession NM\_001711), a gene which is involved in collagen fiber assembly. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BGN. The function of BGN has been established by previous studies. Biglycan, or proteoglycan-I (PG-I), and decorin, or proteoglycan-II (OMIM Ref. No. 125255) are related but distinct small proteoglycans found in many connective tissues. The sequence of the cDNAs encoding the core proteins indicate that the 2 proteins are composed predominantly of a series of 12 tandem repeats of a nominal 24-residue consensus sequence (Fisher et al., 1989). Biglycan is a single-copy gene about 6 kb in length. By Southern analysis of a panel of human-rodent somatic cell hybrid DNAs with cDNA probes, McBride et al. (1990) demonstrated that BGN is located on the X chromosome. By examining hybrids containing spontaneous breaks or well-characterized translocations, they showed that BGN is in the segment Xq13-qter. Fisher et al. (1991) found

that the BGN gene consists of 8 exons including one that encodes the 5-prime untranslated region of the mRNA. The gene promoter lacked both a CAAT and TATA box that was rich in GC content. By in situ hybridization, they localized the gene to Xq27-qter. Traupe et al. (1992) narrowed the assignment to Xq28 in a region proximal to the red/green cone pigment genes (303800, 303900), G6PD (OMIM Ref. No. 305900), and factor VIII (OMIM Ref. No. 306700), and distal to GABRA3 (OMIM Ref. No. 305660). Since the biglycan gene maps to the region where, by comparative gene mapping, one would expect to find the gene for X-linked dominant chondrodysplasia punctata (CDPX2; 302960), it became a candidate gene for that disorder. To test this possibility, Das et al. (1994) analyzed patient samples for mutations in the biglycan gene by SSCP analysis. The small size of the biglycan gene and the availability of its sequence and intron/exon structure (Fisher et al., 1991) made its analysis as a candidate gene relatively straightforward. No mutations were found in 7 unrelated females with chondrodysplasia punctata, 2 of whom had a positive family history and all of whom were clinically consistent with the X-linked dominant form of the disease. Das et al. (1994) excluded biglycan as the site

of the mutation in 2 other disorders that mapped to the same region of the X chromosome. No mutations were found in 9 unrelated patients with dyskeratosis congenita (DKC; 305000), 3 of whom had a family history indicative of X-linked inheritance. Similarly, no mutations were found in the biglycan gene in 8 unrelated females with incontinentia pigmenti (IP2; 308300); 1 had a positive family history and 7 represented sporadic cases. Animal model experiments lend further support to the function of BGN. In vitro studies indicate that biglycan may function in connective tissue metabolism by binding to collagen fibrils and TGF-beta (OMIM Ref. No. 190180), and may promote neuronal survival. To study the role of biglycan in vivo, Xu et al. (1998) generated Bgn-deficient mice. Although apparently normal at birth, these mice displayed a phenotype characterized by reduced growth rate and decreased bone mass. This may be the first report in which deficiency of a noncollagenous extracellular matrix (ECM) protein leads to a skeletal phenotype that is marked by low bone mass that becomes more obvious with age. These mice may serve as an animal model to study the role of ECM proteins in osteoporosis.

[20401] It is appreciated that the abovementioned animal model

for BGN is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20402] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20403] Fisher, L. W.; Termine, J. D.; Young, M. F. : Deduced-protein sequence of bone small proteoglycan I (biglycan) shows homology with proteoglycan II (decorin) and several nonconnective tissue proteins in a variety of species. J. Biol. Chem. 264: 4571–4576, 1989. ; and

[20404] Xu, T.; Bianco, P.; Fisher, L. W.; Longenecker, G.; Smith, E.; Goldstein, S.; Bonadio, J.; Boskey, A.; Heegaard, A.-M.; Sommer, B.; Satomura, K.; Dominguez, P.; Zhao, C.; Kulkarni, A. B.

[20405] Further studies establishing the function and utilities of BGN are found in John Hopkins OMIM database record ID 301870, and in cited publications numbered 9168–9176 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Contactin 2 (axonal) (CNTN2, Accession NM\_005076) is another VGAM430 host target gene. CNTN2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by CNTN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNTN2 BINDING SITE, designated SEQ ID:11524, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20406] Another function of VGAM430 is therefore inhibition of Contactin 2 (axonal) (CNTN2, Accession NM\_005076), a gene which may play a role in axonal growth and cell adhesion. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNTN2. The function of CNTN2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM259.E2F Transcription Factor 1 (E2F1, Accession XM\_097772) is another VGAM430 host target gene. E2F1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by E2F1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of E2F1 BINDING



SITE, designated SEQ ID:41120, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20407] Another function of VGAM430 is therefore inhibition of E2F Transcription Factor 1 (E2F1, Accession XM\_097772), a gene which involved in cell cycle regulation, mediates G1 arrest when bound to Rb. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with E2F1. The function of E2F1 has been established by previous studies. A variety of experimental findings point to the transcription factor E2F as a critical determinant of the G1/S-phase transition during the mammalian cell cycle, serving to activate the transcription of a group of genes that encode proteins necessary for DNA replication. In addition, E2F activity appears to be directly regulated by the action of retinoblastoma protein, and indirectly regulated through the action of G1 cyclins and associated kinases. Ohtani et al. (1995) showed that the accumulation of G1 cyclins is regulated by E2F1. E2F binding sites are found in both the cyclin E (OMIM Ref. No. 123837) and cyclin D1 (OMIM Ref. No. 168461) promoters. Both promoters are activated by E2F gene products, and at least for cyclin E, the E2F sites

contribute to cell cycle-dependent control. They found that the endogenous cyclin E gene is activated following expression of the E2F1 product encoded by a recombinant adenovirus vector. Results were interpreted to suggest the involvement of E2F1 and cyclin E in an autoregulatory loop that governs the accumulation of critical activities affecting the progression of cells through G1. Animal model experiments lend further support to the function of E2F1. The retinoblastoma tumor suppressor protein is a transcriptional repressor that regulates gene expression by physically associating with transcription factors such as members of the E2F family. To address the function of E2F1 and the RB/E2F1 complex in vivo, Yamasaki et al. (1996) and Field et al. (1996) produced mice homozygous for a nonfunctional E2F1 allele. Both groups found that mice lacking E2F1 are viable and fertile. However, Yamasaki et al. (1996) found that they show testicular atrophy and exocrine gland dysplasia, and develop a broad and unusual spectrum of tumors. Although overexpression of E2F1 in tissue culture cells can stimulate cell proliferation and be oncogenic, loss of E2F1 in mice resulted in tumorigenesis, demonstrating that E2F1 also functions as a tumor suppressor. Field et al. (1996) found that E2F1

–/– mice exhibit a defect in T-lymphocyte development, leading to an excess of mature T cells due to a maturation stage-specific defect in thymocyte apoptosis. They also observed aberrant cell proliferation. Weinberg (1996) suggested that the findings of these 2 groups indicate that E2F1 satisfies the definition of a tumor suppressor gene.

[20408] It is appreciated that the abovementioned animal model for E2F1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20409] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20410] Ohtani, K.; DeGregori, J.; Nevins, J. R. : Regulation of the cyclin E gene by transcription factor E2F1. Proc. Nat. Acad. Sci. 92: 12146–12150, 1995. ; and

[20411] Yamasaki, L.; Jacks, T.; Bronson, R.; Goillot, E.; Harlow, E.; Dyson, N. J. : Tumor induction and tissue atrophy in mice lacking E2F-1. Cell 85: 537–548, 1996.

[20412] Further studies establishing the function and utilities of E2F1 are found in John Hopkins OMIM database record ID 189971, and in cited publications numbered 9706–9716, 758–76 and 765–767 listed in the bibliography section

hereinbelow, which are also hereby incorporated by reference. Fucosyltransferase 6 (alpha (1,3) Fucosyltransferase) (FUT6, Accession NM\_000150) is another VGAM430 host target gene. FUT6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FUT6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FUT6 BINDING SITE, designated SEQ ID:5652, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20413] Another function of VGAM430 is therefore inhibition of Fucosyltransferase 6 (alpha (1,3) Fucosyltransferase) (FUT6, Accession NM\_000150), a gene which is involved in the biosynthesis of the e-selectin ligand, sialyl-lewis x. catalyzes the transfer of fucose from gdp- beta-fucose to alpha-2,3 sialylated substrates. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FUT6. The function of FUT6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM194.GRAF (Accession NM\_015071) is another VGAM430 host target gene. GRAF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRAF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRAF BINDING SITE, designated SEQ ID:17447, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20414] Another function of VGAM430 is therefore inhibition of GRAF (Accession NM\_015071), a gene which is a GTPase activating protein for p21-rac. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRAF. The function of GRAF has been established by previous studies. Borkhardt et al. (2000) stated that mutual translocations involving 11q23 in acute leukemias had been demonstrated to show fusion between the mixed lineage leukemia (MLL; 159555) gene and a variety of different partner genes to a total of 23. The detection of a unique t(5;11)(q31;q23) in an infant with juvenile myelomonocytic leukemia and an MLL gene rearrangement provided an

opportunity to clone another MLL fusion partner gene. By cloning the breakpoints in this translocation, Borkhardt et al. (2000) recovered a member of the GTPase-activating protein (GAP) family, which they identified as the human homolog of the avian GRAF gene (Hildebrand et al., 1996). Ishikawa et al. (1998) cloned a GRAF cDNA, which they designated KIAA0621, from a human brain cDNA library and found that it encodes a deduced 753-amino acid protein with a molecular mass of 87 kD. Hildebrand et al. (1996) determined that the GRAF gene is highly homologous to the BCR gene (OMIM Ref. No. 151410), which is also involved in a leukemia-associated translocation. The avian GRAF protein binds to the C-terminal domain of pp125(FAK), one of the tyrosine kinases predicted to be a critical component of the integrin signaling transduction pathway, in an SH3 domain-dependent manner and stimulates the GTPase activity of the GTP-binding protein RhoA. Thus, GRAF acts as a negative regulator of RhoA.

[20415] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20416] Borkhardt, A.; Bojesen, S.; Haas, O. A.; Fuchs, U.; Bartelheimer, D.; Loncarevic, I. F.; Bohle, R. M.; Harbott, J.;

Repp, R.; Jaeger, U.; Viehmann, S.; Henn, T.; Korth, P.; Scharr, D.; Lampert, F. : The human GRAF gene is fused to MLL in a unique t(5;11)(q31;q23) and both alleles are disrupted in three cases of myelodysplastic syndrome/acute myeloid leukemia with a deletion 5q. Proc. Nat. Acad. Sci. 97: 9168–9173, 2000. ; and

[20417] Hildebrand, J. D.; Taylor, J. M.; Parsons, T. J. : An SH3 domain-containing GTPase-activating protein for Rho and Cdc42 associates with focal adhesion kinase. Molec. Cell. Biol. 16: 31.

[20418] Further studies establishing the function and utilities of GRAF are found in John Hopkins OMIM database record ID 605370, and in cited publications numbered 449 and 9440 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Hyperpolarization Activated Cyclic Nucleotide-gated Potassium Channel 4 (HCN4, Accession NM\_005477) is another VGAM430 host target gene. HCN4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HCN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCN4 BIND-

ING SITE, designated SEQ ID:11980, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20419] Another function of VGAM430 is therefore inhibition of Hyperpolarization Activated Cyclic Nucleotide-gated Potassium Channel 4 (HCN4, Accession NM\_005477), a gene which is hyperpolarization activated cyclic nucleotide-gated cation channel 4 and may act as a pacemaker channel in the heart . Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCN4. The function of HCN4 has been established by previous studies. Seifert et al. (1999) demonstrated that heterologous expression of HCN4 produced channels of unusually slow kinetics of activation and inactivation. The mean potential of half-maximal activation was  $-75.2$  mV. The characteristic expression pattern and the sluggish gating suggested to Seifert et al. (1999) that HCN4 controls the rhythmic activity in both thalamocortical neurons and pacemaker cells of the heart. The strong hybridization with testis mRNA further suggested to Seifert et al. (1999) that HCN4 is also expressed in mature spermatozoa or their precursor cells. In this respect, HCN4 may represent



the mammalian equivalent of the HCN channel in the flagellum of sea urchin spermatozoa (Gauss et al., 1998). Seifert et al. (1999) proposed that both the sea urchin channel and the human HCN4 may be involved in the generation of rhythmic activity that controls the waveform of flagellar beating. Sour taste is initiated by protons acting at receptor proteins or channels. Stevens et al. (2001) examined the effects of sour stimuli on taste cells in slices of vallate papilla from rat. From a subset of cells, Stevens et al. (2001) identified a hyperpolarization-activated current that was enhanced by sour stimulation at the taste pore. This current resembled  $I(h)$  found in neurons and cardiomyocytes, a current carried by members of the family of hyperpolarization-activated and cyclic-nucleotide-gated (HCN) channels. Stevens et al. (2001) showed by in situ hybridization and immunohistochemistry that HCN1 and HCN4 are expressed in a subset of taste cells. By contrast, gustducin (OMIM Ref. No. 139395), the G protein involved in bitter and sweet taste, was not expressed in these cells. Stevens et al. (2001) concluded that HCN channels are gated by extracellular protons and may act as receptors for sour taste.

[20420] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [20421] Seifert, R.; Scholten, A.; Gauss, R.; Mincheva, A.; Lichter, P.; Kaupp, U. B. : Molecular characterization of a slowly gating human hyperpolarization-activated channel predominantly expressed in thalamus, heart, and testis. Proc. Nat. Acad. Sci. 96: 9391-9396, 1999. ; and
- [20422] Stevens, D. R.; Seifert, R.; Bufe, B.; Muller, F.; Kremmer, E.; Gauss, R.; Meyerhof, W.; Kaupp, U. B.; Lindemann, B. : Hyperpolarization-activated channels HCN1 and HCN4 mediate respons.
- [20423] Further studies establishing the function and utilities of HCN4 are found in John Hopkins OMIM database record ID 605206, and in cited publications numbered 6813, 765 and 7657 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. MAP-kinase Activating Death Domain (MADD, Accession NM\_003682) is another VGAM430 host target gene. MADD BINDING SITE1 through MADD BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MADD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementar-

ity of the nucleotide sequences of MADD BINDING SITE1 through MADD BINDING SITE6, designated SEQ ID:9787, SEQ ID:28252, SEQ ID:28257, SEQ ID:28236, SEQ ID:28242 and SEQ ID:28247 respectively, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20424] Another function of VGAM430 is therefore inhibition of MAP-kinase Activating Death Domain (MADD, Accession NM\_003682), a gene which may regulate two different pathways for neural activities.interacts with the type-1 tumor necrosis factor receptor (TNFR1); death domain-containing protein. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MADD. The function of MADD has been established by previous studies. Chow and Lee (1996) reported the cDNA sequence of DENN, a novel human gene that is differentially expressed in normal and neoplastic cells (hence, the symbol DENN). Northern blot analysis revealed differential levels of expression of a 6.5-kb DENN transcript in malignant cell lines compared to normal human tissues, where expression was highest in fetal brain and kidney and in adult testis, ovary, brain, and heart. In fetal liver and in several human cancer

cell lines, the authors identified cDNAs representing alternative transcripts of DENN that harbor a deletion of 129 bp encoding 43 amino acids. Present within the serine- and leucine-rich DENN gene product is an arginyl-glycyl-aspartic acid (RGD) cellular adhesion motif and a leucine zipper-like motif. Using the yeast interaction trap system to identify proteins that interact with the death domain of the type 1 tumor necrosis factor receptor (TNFR1; 191190), Schievella et al. (1997) isolated cDNAs encoding 'MAP kinase-activating death domain' (MADD) protein. Immunoblotting of immunoprecipitated proteins from various human cell lines detected an approximately 200-kD MADD protein. The deduced 1,588-amino acid MADD protein contains a C-terminal death domain. The MADD protein associates with TNFR1 through a death domain-death domain interaction. Overexpression of MADD activated the mitogen-activated protein (MAP) kinase ERK2 (OMIM Ref. No. 176948), and expression of the MADD death domain stimulated both the ERK2 and JNK1 (OMIM Ref. No. 601158) MAP kinases and induced the phosphorylation of cytosolic phospholipase A2 (OMIM Ref. No. 600522). The authors suggested that MADD links TNFR1 with MAP kinase activation and arachidonic acid

release. Chow et al. (1998) stated that the DENN and MADD cDNAs and proteins are virtually identical. They found that the DENN gene spans at least 28 kb and is composed of 15 exons, ranging in size from 73 to 1,230 bp, and 14 introns, varying from about 170 bp to 5.3 kb. From genomic studies, they traced the alternative splicing of a 129-bp fragment to an alternative 5-prime donor site involving exon 7. The deduced longer DENN isoform has 1,587 amino acids. Western blot analysis of human MOLT-4 T-lymphoblastic leukemic cell proteins detected a doublet consisting of 138- and 142-kD polypeptides. The authors found the DENN protein concentrated predominantly in the cytosolic compartment of MOLT-4 cells but was restricted to the nuclear compartment of PLC/PRF/5 hepatoma cells

[20425] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20426] Chow, V. T. K.; Lim, K. M.; Lim, D. : The human DENN gene: genomic organization, alternative splicing, and localization to chromosome 11p11.21-p11.22. *Genome* 41: 543-552, 1998. ; and

[20427] Schievella, A. R.; Chen, J. H.; Graham, J. R.; Lin, L.-L. :

MADD, a novel death domain protein that interacts with the type 1 tumor necrosis factor receptor and activates mitogen-activa.

[20428] Further studies establishing the function and utilities of MADD are found in John Hopkins OMIM database record ID 603584, and in cited publications numbered 5841–584 and 1178 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Arginyl Aminopeptidase (aminopeptidase B)–like 1 (RNPEPL1, Accession NM\_018226) is another VGAM430 host target gene. RNPEPL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNPEPL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNPEPL1 BINDING SITE, designated SEQ ID:20160, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20429] Another function of VGAM430 is therefore inhibition of Arginyl Aminopeptidase (aminopeptidase B)–like 1 (RNPEPL1, Accession NM\_018226). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with RNPEPL1. SH3-domain Binding Protein 2 (SH3BP2, Accession NM\_003023) is another VGAM430 host target gene. SH3BP2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SH3BP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SH3BP2 BINDING SITE, designated SEQ ID:8954, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20430] Another function of VGAM430 is therefore inhibition of SH3-domain Binding Protein 2 (SH3BP2, Accession NM\_003023). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SH3BP2. Solute Carrier Family 7 (cationic amino acid transporter,  $\gamma^+$  system), Member 5 (SLC7A5, Accession NM\_003486) is another VGAM430 host target gene. SLC7A5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC7A5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC7A5 BINDING SITE, designated SEQ ID:9579, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20431] Another function of VGAM430 is therefore inhibition of Solute Carrier Family 7 (cationic amino acid transporter,  $\gamma^+$  system), Member 5 (SLC7A5, Accession NM\_003486), a gene which mediates transport of large and small neutral amino acids. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC7A5. The function of SLC7A5 has been established by previous studies. Gaugitsch et al. (1992) cloned a partial human E16 cDNA sequence that was expressed in activated lymphocytes. It was cloned by virtue of its AUUUA rapid degradation signal. Kanai et al. (1998) used expression cloning to isolate a rat cDNA termed LAT1. They showed that LAT1 encoded a protein necessary for system L amino acid transport, thought to be a major route by which cells import large neutral amino acids with branched or aromatic side chains. Mastroberardino et al. (1998) identified the human E16 protein (AF077866) as the first light chain of 4F2



(OMIM Ref. No. 158070), a cell surface glycoprotein, and showed that the resulting heterodimeric complex mediates L-type amino acid transport. Maglott et al. (1994) mapped a gene fragment, EST00889 (OMIM Ref. No. M78741), to chromosome 16 (D16S469E). The map position was refined to 16q24.3 by use of a panel of mouse/human somatic cell hybrids. Maglott et al. (1994) showed that the gene is expressed abundantly in adult lung and liver, and is also expressed in human brain, thymus, retina, and some other tissues.

[20432] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20433] Mastroberardino, L.; Spindler, B.; Pfeiffer, R.; Skelly, P. J.; Loffing, J.; Shoemaker, C. B.; Verrey, F. : Amino-acid transport by heterodimers of 4F2hc/CD98 and members of a permease family. Nature 395: 288–291, 1998. ; and

[20434] Maglott, D. R.; Durkin, A. S.; Lane, S. A.; Callen, D. F.; Feldblyum, T. V.; Nierman, W. C. : The gene for membrane protein E16 (D16S469E) maps to human chromosome 16q24.3 and is expressed.

[20435] Further studies establishing the function and utilities of SLC7A5 are found in John Hopkins OMIM database record

ID 600182, and in cited publications numbered 7345–734 and 8109 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transient Receptor Potential Cation Channel, Subfamily M, Member 8 (TRPM8, Accession NM\_024080) is another VGAM430 host target gene. TRPM8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPM8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPM8 BINDING SITE, designated SEQ ID:23516, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20436] Another function of VGAM430 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily M, Member 8 (TRPM8, Accession NM\_024080), a gene which is thought to form a receptor-activated calcium permeant cation channel. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPM8. The function of TRPM8 and its association with various diseases and clinical conditions, has been established by previous studies,

as described hereinabove with reference to VGAM201. Usher Syndrome 3A (USH3A, Accession NM\_052995) is another VGAM430 host target gene. USH3A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by USH3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USH3A BINDING SITE, designated SEQ ID:27561, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20437] Another function of VGAM430 is therefore inhibition of Usher Syndrome 3A (USH3A, Accession NM\_052995). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USH3A. Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736) is another VGAM430 host target gene. XPR1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by XPR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of XPR1 BINDING SITE, designated SEQ ID:11124, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20438] Another function of VGAM430 is therefore inhibition of Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736), a gene which is a putative G protein-coupled receptor and a target for xenotropic and polytropic murine leukemia retroviruses. Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XPR1. The function of XPR1 has been established by previous studies. There are 4 classes of murine leukemia virus (MLV): xenotropic (X), ecotropic (E), amphotropic (A), and polytropic (P). X- and E-MLV cannot exogenously infect mouse cells and are inherited as part of the mouse genome. While X-MLV can infect other mammalian species but not cells from laboratory mice, A- (see OMIM Ref. No. SLC20A2; 158378) and P-MLV can infect mouse and other species. See Levy (1999) for a review of MLVs. By cloning a human T-lymphocyte cDNA library into a retroviral vector, transducing the library into naturally X-MLV-resistant mouse fibroblasts, and PCR amplification, Tailor et al.

(1999) isolated a cDNA encoding XPR1. Expression of XPR1 in mouse and hamster MLV-resistant fibroblasts rendered the cells susceptible to both X- and P-MLV. The deduced 696-amino acid XPR1 protein contains 8 or 9 potential membrane-spanning regions, 7 potential N-glycosylation sites, and 7 dileucines that may stimulate endocytosis via clathrin-coated pits. Northern blot analysis detected a 4.5-kb XPR1 transcript in all tissues tested, with highest expression in pancreas, kidney, placenta, hematopoietic tissues, and heart, and lowest expression in skeletal muscle. Expression of XPR1 was greater in fetal liver than adult liver. A 9.5-kb XPR1 transcript was also detected in all tissues tested except liver and bone marrow.

[20439] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20440] Levy, J. A. : Xenotropism: the elusive viral receptor finally uncovered. Proc. Nat. Acad. Sci. 96: 802-804, 1999. ; and

[20441] Taylor, C. S.; Nouri, A.; Lee, C. G.; Kozak, C.; Kabat, D. : Cloning and characterization of a cell surface receptor for xenotropic and polytropic murine leukemia viruses. Proc. Nat. Aca.

[20442] Further studies establishing the function and utilities of XPR1 are found in John Hopkins OMIM database record ID 605237, and in cited publications numbered 7484–7487 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. AF311304 (Accession NM\_031214) is another VGAM430 host target gene. AF311304 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AF311304, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AF311304 BINDING SITE, designated SEQ ID:25262, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20443] Another function of VGAM430 is therefore inhibition of AF311304 (Accession NM\_031214). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AF311304. DKFZP566G1424 (Accession XM\_097771) is another VGAM430 host target gene. DKFZP566G1424 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DK–

FZP566G1424, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566G1424 BINDING SITE, designated SEQ ID:41115, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20444] Another function of VGAM430 is therefore inhibition of DKFZP566G1424 (Accession XM\_097771). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566G1424. FBX30 (Accession NM\_033182) is another VGAM430 host target gene. FBX30 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FBX30, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBX30 BINDING SITE, designated SEQ ID:27044, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20445] Another function of VGAM430 is therefore inhibition of FBX30 (Accession NM\_033182). Accordingly, utilities of

VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBX30. FLJ12242 (Accession NM\_024681) is another VGAM430 host target gene. FLJ12242 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12242, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12242 BINDING SITE, designated SEQ ID:23995, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20446] Another function of VGAM430 is therefore inhibition of FLJ12242 (Accession NM\_024681). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12242. FLJ20294 (Accession NM\_017749) is another VGAM430 host target gene. FLJ20294 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20294 BINDING SITE,



designated SEQ ID:19354, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20447] Another function of VGAM430 is therefore inhibition of FLJ20294 (Accession NM\_017749). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20294. FLJ21742 (Accession NM\_032207) is another VGAM430 host target gene. FLJ21742 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21742, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21742 BINDING SITE, designated SEQ ID:25914, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20448] Another function of VGAM430 is therefore inhibition of FLJ21742 (Accession NM\_032207). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21742. FLJ22215 (Accession XM\_173021) is another VGAM430 host target gene. FLJ22215 BINDING SITE is HOST TARGET

binding site found in the 3` untranslated region of mRNA encoded by FLJ22215, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22215 BINDING SITE, designated SEQ ID:46284, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20449] Another function of VGAM430 is therefore inhibition of FLJ22215 (Accession XM\_173021). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22215. HEMK (Accession NM\_016173) is another VGAM430 host target gene. HEMK BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HEMK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HEMK BINDING SITE, designated SEQ ID:18269, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20450] Another function of VGAM430 is therefore inhibition of

HEMK (Accession NM\_016173). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HEMK. KIAA0182 (Accession XM\_050495) is another VGAM430 host target gene. KIAA0182 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0182, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0182 BINDING SITE, designated SEQ ID:35648, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20451] Another function of VGAM430 is therefore inhibition of KIAA0182 (Accession XM\_050495). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0182. KIAA0323 (Accession XM\_032634) is another VGAM430 host target gene. KIAA0323 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0323, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA0323 BINDING SITE, designated SEQ ID:31690, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20452] Another function of VGAM430 is therefore inhibition of KIAA0323 (Accession XM\_032634). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0323. KIAA0415 (Accession XM\_166527) is another VGAM430 host target gene. KIAA0415 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0415, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0415 BINDING SITE, designated SEQ ID:44479, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20453] Another function of VGAM430 is therefore inhibition of KIAA0415 (Accession XM\_166527). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0415. KIAA0420 (Accession XM\_032693) is another

VGAM430 host target gene. KIAA0420 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0420 BINDING SITE, designated SEQ ID:31732, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20454] Another function of VGAM430 is therefore inhibition of KIAA0420 (Accession XM\_032693). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0420. KIAA0556 (Accession XM\_044632) is another VGAM430 host target gene. KIAA0556 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0556 BINDING SITE, designated SEQ ID:34250, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20455] Another function of VGAM430 is therefore inhibition of KIAA0556 (Accession XM\_044632). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0556. KIAA1950 (Accession XM\_166532) is another VGAM430 host target gene. KIAA1950 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1950, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1950 BINDING SITE, designated SEQ ID:44490, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20456] Another function of VGAM430 is therefore inhibition of KIAA1950 (Accession XM\_166532). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1950. KRT6IRS (Accession NM\_033448) is another VGAM430 host target gene. KRT6IRS BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KRT6IRS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KRT6IRS BINDING SITE, designated SEQ ID:27253, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20457] Another function of VGAM430 is therefore inhibition of KRT6IRS (Accession NM\_033448). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KRT6IRS. Matrin 3 (MATR3, Accession NM\_018834) is another VGAM430 host target gene. MATR3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MATR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MATR3 BINDING SITE, designated SEQ ID:20820, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20458] Another function of VGAM430 is therefore inhibition of Matrin 3 (MATR3, Accession NM\_018834). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with MATR3. MGC35558 (Accession NM\_145013) is another VGAM430 host target gene. MGC35558 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC35558, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC35558 BINDING SITE, designated SEQ ID:29620, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20459] Another function of VGAM430 is therefore inhibition of MGC35558 (Accession NM\_145013). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC35558. MGC4415 (Accession NM\_031484) is another VGAM430 host target gene. MGC4415 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4415, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4415 BINDING SITE, designated SEQ ID:25572, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM



RNA, also designated SEQ ID:3141.

[20460] Another function of VGAM430 is therefore inhibition of MGC4415 (Accession NM\_031484). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4415. RAB3A Interacting Protein (rabin3)-like 1 (RAB3IL1, Accession NM\_013401) is another VGAM430 host target gene. RAB3IL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB3IL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB3IL1 BINDING SITE, designated SEQ ID:15064, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20461] Another function of VGAM430 is therefore inhibition of RAB3A Interacting Protein (rabin3)-like 1 (RAB3IL1, Accession NM\_013401). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB3IL1. Splicing Factor, Arginine/serine-rich 5 (SFRS5, Accession NM\_006925) is another VGAM430 host target gene. SFRS5 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRS5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRS5 BINDING SITE, designated SEQ ID:13806, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20462] Another function of VGAM430 is therefore inhibition of Splicing Factor, Arginine/serine-rich 5 (SFRS5, Accession NM\_006925). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRS5. TAF5-like RNA Polymerase II, P300/CBP-associated Factor (PCAF)-associated Factor, 65kDa (TAF5L, Accession NM\_014409) is another VGAM430 host target gene. TAF5L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TAF5L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAF5L BINDING SITE, designated SEQ ID:15752, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3141.

[20463] Another function of VGAM430 is therefore inhibition of TAF5-like RNA Polymerase II, P300/CBP-associated Factor (PCAF)-associated Factor, 65kDa (TAF5L, Accession NM\_014409). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAF5L. LOC150157 (Accession XM\_097823) is another VGAM430 host target gene. LOC150157 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150157, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150157 BINDING SITE, designated SEQ ID:41146, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20464] Another function of VGAM430 is therefore inhibition of LOC150157 (Accession XM\_097823). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150157. LOC152756 (Accession XM\_098262) is another VGAM430 host target gene. LOC152756 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152756, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152756 BINDING SITE, designated SEQ ID:41552, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20465] Another function of VGAM430 is therefore inhibition of LOC152756 (Accession XM\_098262). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152756. LOC196890 (Accession XM\_116951) is another VGAM430 host target gene. LOC196890 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196890, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196890 BINDING SITE, designated SEQ ID:43157, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20466] Another function of VGAM430 is therefore inhibition of

LOC196890 (Accession XM\_116951). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196890. LOC202934 (Accession XM\_117486) is another VGAM430 host target gene. LOC202934 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202934, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202934 BINDING SITE, designated SEQ ID:43466, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20467] Another function of VGAM430 is therefore inhibition of LOC202934 (Accession XM\_117486). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202934. LOC253675 (Accession XM\_172990) is another VGAM430 host target gene. LOC253675 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253675, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC253675 BINDING SITE, designated SEQ ID:46268, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20468] Another function of VGAM430 is therefore inhibition of LOC253675 (Accession XM\_172990). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253675. LOC255465 (Accession XM\_173206) is another VGAM430 host target gene. LOC255465 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255465 BINDING SITE, designated SEQ ID:46458, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20469] Another function of VGAM430 is therefore inhibition of LOC255465 (Accession XM\_173206). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255465. LOC257354 (Accession XM\_170810) is an-

other VGAM430 host target gene. LOC257354 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257354, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257354 BINDING SITE, designated SEQ ID:45585, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20470] Another function of VGAM430 is therefore inhibition of LOC257354 (Accession XM\_170810). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257354. LOC90075 (Accession XM\_028742) is another VGAM430 host target gene. LOC90075 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90075, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90075 BINDING SITE, designated SEQ ID:30741, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20471] Another function of VGAM430 is therefore inhibition of LOC90075 (Accession XM\_028742). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90075. LOC90362 (Accession XM\_031163) is another VGAM430 host target gene. LOC90362 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC90362, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90362 BINDING SITE, designated SEQ ID:31297, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20472] Another function of VGAM430 is therefore inhibition of LOC90362 (Accession XM\_031163). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90362. LOC91461 (Accession XM\_038576) is another VGAM430 host target gene. LOC91461 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC91461, corresponding to a HOST TARGET binding site such as BINDING SITE I,



BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91461 BINDING SITE, designated SEQ ID:32870, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20473] Another function of VGAM430 is therefore inhibition of LOC91461 (Accession XM\_038576). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91461. LOC93259 (Accession XM\_050105) is another VGAM430 host target gene. LOC93259 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC93259, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93259 BINDING SITE, designated SEQ ID:35557, to the nucleotide sequence of VGAM430 RNA, herein designated VGAM RNA, also designated SEQ ID:3141.

[20474] Another function of VGAM430 is therefore inhibition of LOC93259 (Accession XM\_050105). Accordingly, utilities of VGAM430 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC93259. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 431 (VGAM431) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20475] VGAM431 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM431 was detected is described hereinabove with reference to Figs. 1–8.

[20476] VGAM431 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabbit Hemorrhagic Disease Virus. VGAM431 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20477] VGAM431 gene encodes a VGAM431 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM431 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM431 precursor RNA is designated SEQ ID:417, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:417 is located at position 3819 relative to the genome of Rabbit Hemorrhagic Disease Virus.

[20478] VGAM431 precursor RNA folds onto itself, forming VGAM431 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20479] An enzyme complex designated DICER COMPLEX, `dices` the VGAM431 folded precursor RNA into VGAM431 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM431 RNA is designated SEQ ID:3142, and is provided hereinbelow with reference to the sequence listing part.

[20480] VGAM431 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM431 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM431 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20481] VGAM431 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM431 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM431 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM431 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM431 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[20482] The complementary binding of VGAM431 RNA, herein designated VGAM RNA, to host target binding sites on VGAM431 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM431 host target RNA into VGAM431 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20483] It is appreciated that VGAM431 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM431 host target genes. The mRNA of each one of this plurality of VGAM431 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM431 RNA, herein designated VGAM RNA, and which when bound by VGAM431 RNA causes in-

hibition of translation of respective one or more VGAM431 host target proteins.

[20484] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM431 gene, herein designated VGAM GENE, on one or more VGAM431 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20485] It is yet further appreciated that a function of VGAM431 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM431 include diagnosis, prevention and

treatment of viral infection by Rabbit Hemorrhagic Disease Virus. Specific functions, and accordingly utilities, of VGAM431 correlate with, and may be deduced from, the identity of the host target genes which VGAM431 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20486] Nucleotide sequences of the VGAM431 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM431 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM431 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM431 are further described hereinbelow with reference to Table 1.

[20487] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM431 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM431 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20488] As mentioned hereinabove with reference to Fig. 1, a function of VGAM431 gene, herein designated VGAM is inhibition of expression of VGAM431 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM431 correlate with, and may be deduced from, the identity of the target genes which VGAM431 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20489] BCL2-like 2 (BCL2L2, Accession NM\_004050) is a VGAM431 host target gene. BCL2L2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL2L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2L2 BINDING SITE, designated SEQ ID:10261, to the nucleotide sequence of VGAM431 RNA, herein designated VGAM RNA, also designated SEQ ID:3142.

[20490] A function of VGAM431 is therefore inhibition of BCL2-like 2 (BCL2L2, Accession NM\_004050), a gene which promotes cell survival. Accordingly, utilities of VGAM431 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL2L2. The function of BCL2L2 has been established by previous studies. Gibson et al. (1996) used degenerate PCR to clone a novel BCL2 homolog which they denoted BCLW. The



gene encodes a 193–amino acid polypeptide. Gibson et al. (1996) also isolated the mouse BCLW gene; its amino acid sequence is 99% identical to that of the human gene.

Mouse BCLW is expressed as a 3.7–kb mRNA in a variety of tissues, with highest expression in brain, colon, and salivary gland. In mouse hematopoietic cell lines, BCLW is expressed in myeloid cells and to a lesser extent in lymphoid cells. Like BCL2, expressed BCLW promotes cell survival under a variety of cytotoxic conditions. Gibson et al. (1996) used fluorescence in situ hybridization to map the BCLW gene to human chromosome 14q11.2–q12. Animal model experiments lend further support to the function of BCL2L2. To identify genes required for mammalian spermatogenesis, Ross et al. (1998) screened lines of mutant mice created using a retroviral gene–trap system for male infertility. Homozygous ROSA41 male mice exhibited sterility associated with progressive testicular degeneration. Germ cell defects were first observed at 19 days postnatal. Spermatogenesis was blocked during late spermiogenesis in young adults. Gradual depletion of all stages of germ cells resulted in a Sertoli–cell–only phenotype by approximately 6 months of age. Subsequently, almost all Sertoli cells were lost from the seminiferous

tubules, and the Leydig cell population was reduced. Molecular analysis indicated that the gene mutated in these mice is BCLW, a death-protecting member of the Bcl2 family. The mutant allele of Bclw in ROSA41 did not produce a Bclw polypeptide. Expression of Bclw in the testis appeared to be restricted to elongating spermatids and Sertoli cells.

[20491] It is appreciated that the abovementioned animal model for BCL2L2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20492] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20493] Gibson, L.; Holmgreen, S. P.; Huang, D. C. S.; Bernard, O.; Copeland, N. G.; Jenkins, N. A.; Sutherland, G. R.; Baker, E.; Adams, J. M.; Cory, S. : bcl-w, a novel member of the bcl-2 family, promotes cell survival. *Oncogene* 13: 665-675, 1996. ; and

[20494] Ross, A. J.; Waymire, K. G.; Moss, J. E.; Parlow, A. F.; Skinner, M. K.; Russell, L. D.; MacGregor, G. R. : Testicular degeneration in Bclw-deficient mice. *Nature Genet.* 18: 251-256, 1999.

[20495] Further studies establishing the function and utilities of BCL2L2 are found in John Hopkins OMIM database record ID 601931, and in cited publications numbered 6256–6257 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Reserved (C8orf13, Accession XM\_088377) is another VGAM431 host target gene. C8orf13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C8orf13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C8orf13 BINDING SITE, designated SEQ ID:39655, to the nucleotide sequence of VGAM431 RNA, herein designated VGAM RNA, also designated SEQ ID:3142.

[20496] Another function of VGAM431 is therefore inhibition of Reserved (C8orf13, Accession XM\_088377). Accordingly, utilities of VGAM431 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C8orf13. Opiate Receptor-like 1 (OPRL1, Accession NM\_000913) is another VGAM431 host target gene. OPRL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OPRL1,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OPRL1 BINDING SITE, designated SEQ ID:6613, to the nucleotide sequence of VGAM431 RNA, herein designated VGAM RNA, also designated SEQ ID:3142.

[20497] Another function of VGAM431 is therefore inhibition of Opiate Receptor-like 1 (OPRL1, Accession NM\_000913). Accordingly, utilities of VGAM431 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OPRL1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 432 (VGAM432) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20498] VGAM432 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM432 was detected is described hereinabove with reference to Figs. 1–8.

[20499] VGAM432 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabbit Hemorrhagic Dis–

ease Virus. VGAM432 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20500] VGAM432 gene encodes a VGAM432 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM432 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM432 precursor RNA is designated SEQ ID:418, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:418 is located at position 3603 relative to the genome of Rabbit Hemorrhagic Disease Virus.

[20501] VGAM432 precursor RNA folds onto itself, forming VGAM432 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20502] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM432 folded precursor RNA into VGAM432 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM432 RNA is designated SEQ ID:3143, and is provided hereinbelow with reference to the sequence listing part.

[20503] VGAM432 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM432 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM432 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20504] VGAM432 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM432 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM432 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM432 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM432 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20505] The complementary binding of VGAM432 RNA, herein designated VGAM RNA, to host target binding sites on VGAM432 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM432 host target RNA into VGAM432 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20506] It is appreciated that VGAM432 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM432 host target genes. The mRNA of each one of this plurality of VGAM432 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM432 RNA, herein designated VGAM RNA, and which when bound by VGAM432 RNA causes inhibition of translation of respective one or more VGAM432 host target proteins.

[20507] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM432 gene, herein designated VGAM GENE, on one or more VGAM432 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are



also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20508] It is yet further appreciated that a function of VGAM432 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of viral infection by Rabbit Hemorrhagic Disease Virus. Specific functions, and accordingly utilities, of VGAM432 correlate with, and may be deduced from, the identity of the host target genes which VGAM432 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20509] Nucleotide sequences of the VGAM432 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM432 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM432 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM432 are further described hereinbelow with reference to Table 1.

[20510] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM432 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM432 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20511] As mentioned hereinabove with reference to Fig. 1, a function of VGAM432 gene, herein designated VGAM is inhibition of expression of VGAM432 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM432 correlate with, and may be deduced from, the identity of the target genes which VGAM432 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20512] Cadherin, EGF LAG Seven-pass G-type Receptor 2 (flamingo homolog, Drosophila) (CELSR2, Accession NM\_001408) is a VGAM432 host target gene. CELSR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CELSR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of CELSR2 BINDING SITE, designated SEQ ID:7109, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20513] A function of VGAM432 is therefore inhibition of Cadherin, EGF LAG Seven-pass G-type Receptor 2 (flamingo homolog, Drosophila) (CELSR2, Accession NM\_001408), a gene which is a calcium dependent cell adhesion protein. Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CELSR2. The function of CELSR2 has been established by previous studies. The domain that characterizes epidermal growth factor (EGF; 131530) consists of approximately 50 amino acids with 3 disulfide bonds. EGF-like domains are believed to play a critical role in a number of extracellular events, including cell adhesion and receptor-ligand interactions. Proteins with EGF-like domains often consist of more than 1,000 amino acids, have multiple copies of the EGF-like domain, and contain additional domains known to be involved in specific protein-protein interactions. To identify proteins containing EGF-like domains, Nakayama et al. (1998) searched a database of long cDNA sequences randomly selected from a human brain cDNA library for those that encode an EGF-

like motif. They identified several partial cDNAs encoding novel proteins with EGF-like domains, such as EGFL2, which they named MEGF3. The predicted partial EGFL2 protein has at least 5 cadherin motifs, 6 EGF-like domains, 2 laminin G domains (see OMIM Ref. No. 601033), 7 transmembrane domains, and a cytoplasmic proline-rich sequence. Human EGFL2 appears to have a domain structure identical to that of rat Megf2 (OMIM Ref. No. 604264), whose complete coding sequence was also isolated by the authors. Northern blot analysis detected rat Megf3 expression in several regions of the brain.

[20514] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20515] Nagase, T.; Seki, N.; Ishikawa, K.; Ohira, M.; Kwarabayasi, Y.; Ohara, O.; Tanaka, A.; Kotani, H.; Miyajima, N.; Nomura, N. : Prediction of the coding sequences of unidentified human genes. VI. The coding sequences of 80 new genes (KIAA0201-KIAA0280) deduced by analysis of cDNA clones from cell line KG-1 and brain. DNA Res. 3: 321-329, 1996. ; and

[20516] Nakayama, M.; Nakajima, D.; Nagase, T.; Nomura, N.; Seki, N.; Ohara, O. : Identification of high-molecular-weight

proteins with multiple EGF-like motifs by motif-trap screening. Genomic.

[20517] Further studies establishing the function and utilities of CELSR2 are found in John Hopkins OMIM database record ID 604265, and in cited publications numbered 9379 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Egl Nine Homolog 2 (C. elegans) (EGLN2, Accession NM\_080732) is another VGAM432 host target gene. EGLN2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EGLN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGLN2 BINDING SITE, designated SEQ ID:28022, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20518] Another function of VGAM432 is therefore inhibition of Egl Nine Homolog 2 (C. elegans) (EGLN2, Accession NM\_080732), a gene which is an essential component of the pathway. Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN2. The function of

EGLN2 has been established by previous studies. In cultured mammalian cells, Bruick and McKnight (2001) found that the inappropriate accumulation of HIF caused by forced expression of the HIF1- $\alpha$  subunit under normoxic conditions was attenuated by coexpression of HPH. Suppression of HPH in cultured *Drosophila melanogaster* cells by RNA interference resulted in elevated expression of the hypoxia-inducible gene LDH (see OMIM Ref. No. 150000) under normoxic conditions. Bruick and McKnight (2001) concluded that HPH is an essential component of the pathway through which cells sense oxygen. HIF is a transcriptional complex that plays a central role in mammalian oxygen homeostasis. Posttranslational modification by prolyl hydroxylation is a key regulatory event that targets HIF- $\alpha$  (HIF1; 603348) subunits for proteasomal destruction via the von Hippel-Lindau (VHL; 193300) ubiquitylation complex. Epstein et al. (2001) defined a conserved HIF-VHL-prolyl hydroxylase pathway in *C. elegans* and identified Egl9 as a dioxygenase that regulates HIF by prolyl hydroxylation. In mammalian cells, they showed that the HIF-prolyl hydroxylases are represented by 3 proteins with a conserved 2-histidine-1-carboxylate iron coordination motif at the catalytic site. The genes en-

coding these proteins were cloned and termed PHD1, PHD2 (OMIM Ref. No. 606425), and PHD3 (OMIM Ref. No. 606426) by the authors. Direct modulation of recombinant enzyme activity by graded hypoxia, iron chelation, and cobaltous ions mirrored the characteristics of HIF induction in vivo, fulfilling requirements for these enzymes being oxygen sensors that regulate HIF.

[20519] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20520] Bruick, R. K.; McKnight, S. L. : A conserved family of prolyl-4-hydroxylases that modify HIF. Science 294: 1337-1340, 2001. ; and

[20521] Epstein, A. C. R.; Gleadle, J. M.; McNeill, L. A.; Hewitson, K. S.; O'Rourke, J.; Mole, D. R.; Mukherji, M.; Metzen, E.; Wilson, M. I.; Dhanda, A.; Tian, Y.-M.; Masson, N.; Hamilton, D.

[20522] Further studies establishing the function and utilities of EGLN2 are found in John Hopkins OMIM database record ID 606424, and in cited publications numbered 4543-4544 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Frizzled Homolog 1 (Drosophila) (FZD1, Accession NM\_003505) is

another VGAM432 host target gene. FZD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FZD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FZD1 BINDING SITE, designated SEQ ID:9594, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20523] Another function of VGAM432 is therefore inhibition of Frizzled Homolog 1 (Drosophila) (FZD1, Accession NM\_003505), a gene which may be involved in bone resorption; strongly similar to rat Fzd. Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FZD1. The function of FZD1 has been established by previous studies. Members of the 'frizzled' (Fz) gene family encode 7-transmembrane domain proteins that are receptors for Wnt (see OMIM Ref. No. 164975) signaling proteins. See 601766. Liu et al. (2001) constructed a chimeric receptor with the ligand-binding and transmembrane segments from the beta-2-adrenergic receptor (OMIM Ref. No. 109690) and the cytoplasmic domains from rat frizzled-1.



Stimulation of mouse F9 clones expressing the chimera with the beta-adrenergic agonist isoproterenol stimulated stabilization of beta-catenin (OMIM Ref. No. 116806), activation of a beta-catenin-sensitive promoter, and formation of primitive endoderm. The response was blocked by inactivation of pertussis toxin-sensitive, heterotrimeric G proteins, and by depletion of G-alpha-q (OMIM Ref. No. 600998) and G-alpha-o (OMIM Ref. No. 139311). Thus, Liu et al. (2001) concluded that G proteins are elements of Wnt/frizzled-1 signaling to the beta-catenin-lymphoid-enhancer factor (LEF)-T-cell factor (Tcf) pathway.

[20524] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20525] Liu, T.; DeCostanzo, A. J.; Liu, X.; Wang, H.; Hallagan, S.; Moon, R. T.; Malbon, C. C. : G protein signaling from activated rat frizzled-1 to the beta-catenin-Lef-Tcf pathway. Science 292: 1718-1722, 2001. ; and

[20526] Sagara, N.; Toda, G.; Hirai, M.; Terada, M.; Katoh, M. : Molecular cloning, differential expression, and chromosomal localization of human frizzled-1, frizzled-2, and frizzled-7. Bioch.

[20527] Further studies establishing the function and utilities of FZD1 are found in John Hopkins OMIM database record ID 603408, and in cited publications numbered 5301–5302 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ATP6V1EL2 (Accession NM\_080653) is another VGAM432 host target gene. ATP6V1EL2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ATP6V1EL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP6V1EL2 BINDING SITE, designated SEQ ID:27941, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20528] Another function of VGAM432 is therefore inhibition of ATP6V1EL2 (Accession NM\_080653). Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP6V1EL2. FLJ00001 (Accession XM\_088525) is another VGAM432 host target gene. FLJ00001 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ00001, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ00001 BINDING SITE, designated SEQ ID:39789, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20529] Another function of VGAM432 is therefore inhibition of FLJ00001 (Accession XM\_088525). Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00001. KIAA0628 (Accession NM\_014789) is another VGAM432 host target gene. KIAA0628 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0628, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0628 BINDING SITE, designated SEQ ID:16676, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20530] Another function of VGAM432 is therefore inhibition of KIAA0628 (Accession NM\_014789). Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0628. KIAA0652 (Accession NM\_014741) is another VGAM432 host target gene. KIAA0652 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0652, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0652 BINDING SITE, designated SEQ ID:16411, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20531] Another function of VGAM432 is therefore inhibition of KIAA0652 (Accession NM\_014741). Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0652. KIAA1389 (Accession XM\_045839) is another VGAM432 host target gene. KIAA1389 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1389, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1389 BINDING SITE, designated SEQ ID:34570, to the

nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20532] Another function of VGAM432 is therefore inhibition of KIAA1389 (Accession XM\_045839). Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1389. KIAA1889 (Accession XM\_056298) is another VGAM432 host target gene. KIAA1889 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1889, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1889 BINDING SITE, designated SEQ ID:36390, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20533] Another function of VGAM432 is therefore inhibition of KIAA1889 (Accession XM\_056298). Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1889. MGC29654 (Accession XM\_039448) is another VGAM432 host target gene. MGC29654 BINDING SITE is HOST TARGET binding site found in the 5' untranslated

region of mRNA encoded by MGC29654, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC29654 BINDING SITE, designated SEQ ID:33094, to the nucleotide sequence of VGAM432 RNA, herein designated VGAM RNA, also designated SEQ ID:3143.

[20534] Another function of VGAM432 is therefore inhibition of MGC29654 (Accession XM\_039448). Accordingly, utilities of VGAM432 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC29654. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 433 (VGAM433) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20535] VGAM433 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM433 was detected is described hereinabove with reference to Figs. 1–8.

[20536] VGAM433 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Rabbit Hemorrhagic Disease Virus. VGAM433 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20537] VGAM433 gene encodes a VGAM433 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM433 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM433 precursor RNA is designated SEQ ID:419, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:419 is located at position 1022 relative to the genome of Rabbit Hemorrhagic Disease Virus.

[20538] VGAM433 precursor RNA folds onto itself, forming VGAM433 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20539] An enzyme complex designated DICER COMPLEX, `dices` the VGAM433 folded precursor RNA into VGAM433 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM433 RNA is designated SEQ ID:3144, and is provided hereinbelow with reference to the sequence listing part.

[20540] VGAM433 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM433 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM433 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20541] VGAM433 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM433 host target RNA, herein designated VGAM HOST TARGET RNA. This



complementary binding is due to the fact that the nucleotide sequence of VGAM433 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM433 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM433 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20542] The complementary binding of VGAM433 RNA, herein designated VGAM RNA, to host target binding sites on VGAM433 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM433 host tar-

get RNA into VGAM433 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20543] It is appreciated that VGAM433 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM433 host target genes. The mRNA of each one of this plurality of VGAM433 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM433 RNA, herein designated VGAM RNA, and which when bound by VGAM433 RNA causes inhibition of translation of respective one or more VGAM433 host target proteins.

[20544] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM433 gene, herein designated VGAM GENE, on one or more VGAM433 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20545] It is yet further appreciated that a function of VGAM433 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of viral infection by Rabbit Hemorrhagic Disease Virus. Specific functions, and accordingly utilities, of VGAM433 correlate with, and may be deduced from, the identity of the host target genes which VGAM433 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20546] Nucleotide sequences of the VGAM433 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM433 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM433 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM433 are further

described hereinbelow with reference to Table 1.

[20547] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM433 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM433 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20548] As mentioned hereinabove with reference to Fig. 1, a function of VGAM433 gene, herein designated VGAM is inhibition of expression of VGAM433 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM433 correlate with, and may be deduced from, the identity of the target genes which VGAM433 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20549] B-cell CLL/lymphoma 10 (BCL10, Accession NM\_003921) is a VGAM433 host target gene. BCL10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL10 BIND-

ING SITE, designated SEQ ID:10007, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20550] A function of VGAM433 is therefore inhibition of B-cell CLL/lymphoma 10 (BCL10, Accession NM\_003921), a gene which is a positive regulator of lymphocyte proliferation, NF-kappaB activator. Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL10. The function of BCL10 has been established by previous studies. B-cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas) are the most common form of lymphoma arising in extranodal sites, in most cases arising in the gastric mucosa (Isaacson and Spencer, 1995). Cytogenetic studies of low-grade malignant MALT lymphoma identified abnormalities of chromosome 1p22, in particular translocation t(1;14)(p22;q32), as uncommon but recurrent events (Wotherspoon et al., 1992). Willis et al. (1999) cloned a t(1;14)(p22;q32) translocation breakpoint from a case of low-grade MALT lymphoma and identified a recurrent breakpoint upstream of the promoter of a novel gene, BCL10. The BCL10 gene encodes a predicted protein of 233 amino acids and is a cellular homolog of

the equine herpesvirus-2 gene (E10); both contain an amino-terminal caspase recruitment domain (CARD) homologous to that found in several apoptotic molecules. BCL10 was found to be expressed as a transcript of 4.2 kb in all normal and malignant tissues examined. BCL10 and E10 activated nuclear factor kappa-B (NFkB; 164011) but caused apoptosis of 293 cells. BCL10 expressed in a MALT lymphoma exhibited a frameshift mutation resulting in truncation distal to the CARD. Truncated BCL10 activated NFkB but did not induce apoptosis. Wildtype BCL10 suppressed transformation, whereas mutant forms had lost this activity and displayed gain-of-function transforming activity. Animal model experiments lend further support to the function of BCL10. Ruland et al. (2001) showed that one-third of Bcl10  $-/-$  mouse embryos developed exencephaly, leading to embryonic lethality. Surprisingly, Bcl10  $-/-$  cells retained susceptibility to various apoptotic stimuli in vivo and in vitro. However, surviving Bcl10  $-/-$  mice were severely immunodeficient, and Bcl10  $-/-$  lymphocytes were defective in antigen receptor or phorbol myristate acetate (PMA)/ionomycin-induced activation. Early tyrosine phosphorylation, mitogen-activated protein kinase (MAPK; OMIM Ref. No. 604921) and activator protein-1

(AP1; 165160) activation, and calcium signaling were normal in mutant lymphocytes, but antigen receptor-induced NFkB activation was absent. Thus, the authors concluded that BCL10 functions as a positive regulator of lymphocyte proliferation that specifically connects antigen receptor signaling in B and T cells to NFkB activation.

[20551] It is appreciated that the abovementioned animal model for BCL10 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20552] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20553] Willis, T. G.; Jadayel, D. M.; Du, M.-Q.; Peng, H.; Perry, A. R.; Abdul-Rauf, M.; Price, H.; Karran, L.; Majekodunmi, O.; Wlodarska, I.; Pan, L.; Crook, T.; Hamoudi, R.; Isaacson, P. G.; Dyer, M. J. S. : Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types Cell 96: 35-45, 1999. ; and

[20554] Ruland, J.; Duncan, G. S.; Elia, A.; del Barco Barrantes, I.; Nguyen, L.; Plyte, S.; Millar, D. G.; Bouchard, D.; Wakeham, A.; Ohashi, P. S.; Mak, T. W. : Bcl10 is a positive regulator.

[20555] Further studies establishing the function and utilities of

BCL10 are found in John Hopkins OMIM database record ID 603517, and in cited publications numbered 11497–8668 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Leucine–zipper–like Transcriptional Regulator, 1 (LZTR1, Accession NM\_006767) is another VGAM433 host target gene. LZTR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LZTR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LZTR1 BINDING SITE, designated SEQ ID:13642, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20556] Another function of VGAM433 is therefore inhibition of Leucine–zipper–like Transcriptional Regulator, 1 (LZTR1, Accession NM\_006767). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LZTR1. Protocadherin 11 X-linked (PCDH11X, Accession NM\_032968) is another VGAM433 host target gene. PCDH11X BINDING SITE1 and PCDH11X BINDING SITE2 are HOST TARGET



binding sites found in untranslated regions of mRNA encoded by PCDH11X, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDH11X BINDING SITE1 and PCDH11X BINDING SITE2, designated SEQ ID:26793 and SEQ ID:26808 respectively, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20557] Another function of VGAM433 is therefore inhibition of Protocadherin 11 X-linked (PCDH11X, Accession NM\_032968), a gene which is thought to play a fundamental role in cell-cell recognition essential for the segmental development and function of the central nervous system. Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH11X. The function of PCDH11X has been established by previous studies. The protocadherins are a subfamily of calcium-dependent cell adhesion and recognition proteins of the cadherin superfamily. They are particularly prevalent in the central nervous system. By database searching with a human PCDH7 (OMIM Ref. No. 602988) cDNA probe, Yoshida and Sugano

(1999) identified a homologous mRNA from infant brain. They found the same sequence on a genomic clone of chromosome X, within the X–Y homology region at Xp21.3. By RT–PCR using fetal brain, they identified a cDNA, PCDH11, which they called PCDHX, encoding a deduced 1,021–amino acid protein. Sequence analysis predicted a 25–amino acid signal peptide, an extracellular portion with 7 cadherin repeats, a 24–amino acid trans–membrane stretch, and a 10–amino acid cytoplasmic domain with homology to PCDH1 (OMIM Ref. No. 603626) and PCDH7. Yoshida and Sugano (1999) also identified a splice variant, termed PCDHXb, by EST database searches. Northern blot analysis revealed expression of an approximately 6.0–kb transcript in human and mouse fetal brain. Using STS analysis, Yoshida and Sugano (1999) mapped the PCDH11 gene to the X–Y homology region at chromosome Xq21.3 that is homologous to Yp11.1. Blanco et al. (2000) mapped the PCDH11 gene to Xq21.3, within the X–Y homologous region, using detailed YAC and PAC contigs and fine STS marker order.

[20558] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [20559] Yoshida, K.; Sugano, S. : Identification of a novel proto-cadherin gene (PCDH11) on the human XY homology region in Xq21.3. Genomics 62: 540–543, 1999. ; and
- [20560] Yoshida, K.; Sugano, S. : Identification of a novel proto-cadherin gene (PCDH11) on the human XY homology region in Xq21.3. Genomics 62: 540–543, 1999.
- [20561] Further studies establishing the function and utilities of PCDH11X are found in John Hopkins OMIM database record ID 300246, and in cited publications numbered 9161–916 and 9178 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RAB1A, Member RAS Oncogene Family (RAB1A, Accession XM\_046674) is another VGAM433 host target gene. RAB1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB1A BINDING SITE, designated SEQ ID:34791, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.
- [20562] Another function of VGAM433 is therefore inhibition of

RAB1A, Member RAS Oncogene Family (RAB1A, Accession XM\_046674), a gene which is involved in vesicle transport. Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB1A. The function of RAB1A has been established by previous studies. RAB proteins have been postulated to regulate the targeting and fusion of membranous vesicles during organelle assembly and transport. RAB proteins undergo regulated exchange of GTP for GDP, and they slowly hydrolyze the bound GTP in a reaction that is thought to regulate the timing and unidirectional nature of these assembly events. All of the known RAB proteins terminate in sequences such as cys-X-cys (e.g., RAB3A, 179490), cys-cys (e.g., RAB1A), or a closely related sequence, and all are believed to be geranylgeranylated. From a human pheochromocytoma cDNA library, Zahraoui et al. (1989) isolated 7 cDNA clones corresponding to genes encoding the Ras-associated GTP-binding proteins. See RAB5A (OMIM Ref. No. 179512). The predicted 205-amino acid human and rat RAB1 proteins are identical and share 75% identity with YPT1, the *S. cerevisiae* homolog. Northern blot analysis revealed that the RAB1 gene was expressed as a major (OMIM Ref. No. 2.7

kb) and a minor (OMIM Ref. No. 1.7 kb) mRNA in a human fibroblast cell line. The 'wobbler' spinal muscular atrophy gene (wr) maps to proximal mouse chromosome 11, tightly linked to Rab1 and Glns-ps1, an intronless pseudogene of the glutamine synthetase gene (OMIM Ref. No. 138290). Wedemeyer et al. (1996) used these markers to construct a 1.3-Mb YAC contig of the Rab1 region on mouse chromosome 11. Two overlapping YACS were identified that contained a 150-kb region of human chromosome 2p, comprising the RAB1 locus as well as a newly discovered STS (OMIM Ref. No. AHY1.1) and a trapped exon (OMIM Ref. No. ETG1.1). The region was mapped to 2p14-p13.4 using somatic cell hybrids and a radiation hybrid panel, thus extending a known region of conserved synteny between mouse chromosome 11 and human 2p. The gene for limb-girdle muscular dystrophy type 2B (LGMD2B; 253601) maps to 2p16-p13. The authors noted that conservation between the mouse Rab1 and human RAB1 regions will be helpful in identifying candidate genes for the 'wobbler' spinal muscular atrophy and in clarifying a possible relationship between wr and LGMD2B.

[20563] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [20564] Allan, B. B.; Moyer, B. D.; Balch, W. E. : Rab1 recruitment of p115 into a cis-SNARE complex: programming budding COPII vesicles for fusion. Science 289: 444-448, 2000. ; and
- [20565] Wedemeyer, N.; Lengeling, A.; Ronsiek, M.; Korthaus, D.; Baer, K.; Wuttke, M.; Jockusch, H. : YAC contigs of the Rab1 and wobbler (wr) spinal muscular atrophy gene region on proximal mo.
- [20566] Further studies establishing the function and utilities of RAB1A are found in John Hopkins OMIM database record ID 179508, and in cited publications numbered 2537-253 and 2722 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Thromboxane A2 Receptor (TBXA2R, Accession NM\_001060) is another VGAM433 host target gene. TBXA2R BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TBXA2R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBXA2R BINDING SITE, designated SEQ ID:6727, to the nucleotide sequence of VGAM433 RNA,

herein designated VGAM RNA, also designated SEQ ID:3144.

[20567] Another function of VGAM433 is therefore inhibition of Thromboxane A2 Receptor (TBXA2R, Accession NM\_001060), a gene which activates  $\text{Ca}^{2+}$ -activated chloride channels; stimulates platelet aggregation and smooth muscle constriction. Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TBXA2R. The function of TBXA2R has been established by previous studies. Thromboxane A2 (TXA2), an arachidonate metabolite, is a potent stimulator of platelet aggregation and a constrictor of vascular and respiratory smooth muscles. It has been implicated as a mediator in diseases such as myocardial infarction, stroke, and bronchial asthma. Ushikubi et al. (1989) purified the cell surface receptor for TXA2, using a stable analog of TXA2. Using an oligonucleotide probe corresponding to its partial amino acid sequence, Hirata et al. (1991) obtained a cDNA encoding the receptor from human placenta and a partial cDNA clone from cultured human megakaryocytic leukemia cells. The placenta cDNA encoded a protein of 343 amino acids with 7 putative transmembrane domains. The protein ex-

pressed in COS-7 cells bound drugs with affinities identical to those of the platelet receptor, and that expressed in *Xenopus* oocytes opened calcium-ion-activated chloride channels on agonist stimulation. Northern blot analysis and nucleotide sequences of the 2 clones suggested that an identical form of thromboxane A<sub>2</sub> receptor is present in platelets and vascular tissues. Animal model experiments lend further support to the function of TBXA<sub>2</sub>R. The actions of TXA<sub>2</sub> are mediated by G protein-coupled thromboxane-prostanoid (TP) receptors. TP receptors have been implicated in the pathogenesis of cardiovascular diseases. To investigate the physiologic functions of TP receptors, Thomas et al. (1998) generated TP receptor-deficient mice by gene targeting. *Tp* <sup>-/-</sup> animals reproduced and survived in expected numbers, and their major organ systems were normal. Thromboxane agonist binding could not be detected in tissues from *Tp* <sup>-/-</sup> mice. Bleeding times were prolonged in these mice and their platelets did not aggregate after exposure to TXA<sub>2</sub> agonists. Aggregation responses after collagen stimulation were also delayed, although ADP-stimulated aggregation was normal. In summary, *Tp* <sup>-/-</sup> mice had a mild bleeding disorder and altered vascular responses to TXA<sub>2</sub> and



arachidonic acid. Their studies suggested that most of the recognized functions of TXA2 are mediated by the single known Tp gene locus.

[20568] It is appreciated that the abovementioned animal model for TBXA2R is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[20569] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20570] Hirata, M.; Hayashi, Y.; Ushikubi, F.; Yokota, Y.; Kageyama, R.; Nakanishi, S.; Narumiya, S. : Cloning and expression of cDNA for a human thromboxane A2 receptor. Nature 349: 617-620, 1991. ; and

[20571] Thomas, D. W.; Mannon, R. B.; Mannon, P. J.; Latour, A.; Oliver, J. A.; Hoffman, M.; Smithies, O.; Koller, B. H.; Coffman, T. M. : Coagulation defects and altered hemodynamic responses.

[20572] Further studies establishing the function and utilities of TBXA2R are found in John Hopkins OMIM database record ID 188070, and in sited publications numbered 9654, 10839-9657, 9678-9679, 10598, 1084 and 9684-9683 listed in the bibliography section hereinbelow, which are

also hereby incorporated by reference. Chromosome 21 Open Reading Frame 18 (C21orf18, Accession NM\_017438) is another VGAM433 host target gene. C21orf18 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C21orf18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C21orf18 BINDING SITE, designated SEQ ID:18898, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20573] Another function of VGAM433 is therefore inhibition of Chromosome 21 Open Reading Frame 18 (C21orf18, Accession NM\_017438). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C21orf18. Caspase 9, Apoptosis-related Cysteine Protease (CASP9, Accession NM\_001229) is another VGAM433 host target gene. CASP9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CASP9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2

illustrates the complementarity of the nucleotide sequences of CASP9 BINDING SITE, designated SEQ ID:6899, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20574] Another function of VGAM433 is therefore inhibition of Caspase 9, Apoptosis-related Cysteine Protease (CASP9, Accession NM\_001229). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CASP9. FLJ20813 (Accession NM\_017961) is another VGAM433 host target gene. FLJ20813 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20813, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20813 BINDING SITE, designated SEQ ID:19680, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20575] Another function of VGAM433 is therefore inhibition of FLJ20813 (Accession NM\_017961). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20813.

G Protein-coupled Receptor 64 (GPR64, Accession NM\_005756) is another VGAM433 host target gene. GPR64 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR64, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR64 BINDING SITE, designated SEQ ID:12316, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20576] Another function of VGAM433 is therefore inhibition of G Protein-coupled Receptor 64 (GPR64, Accession NM\_005756). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR64. HTGN29 (Accession NM\_020199) is another VGAM433 host target gene. HTGN29 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HTGN29, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HTGN29 BINDING SITE, designated SEQ

ID:21433, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20577] Another function of VGAM433 is therefore inhibition of HTGN29 (Accession NM\_020199). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTGN29. KIAA0352 (Accession NM\_014830) is another VGAM433 host target gene. KIAA0352 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0352, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0352 BINDING SITE, designated SEQ ID:16827, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20578] Another function of VGAM433 is therefore inhibition of KIAA0352 (Accession NM\_014830). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0352. KIAA0757 (Accession NM\_006038) is another VGAM433 host target gene. KIAA0757 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0757, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0757 BINDING SITE, designated SEQ ID:12672, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20579] Another function of VGAM433 is therefore inhibition of KIAA0757 (Accession NM\_006038). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0757. KIAA1796 (Accession XM\_166146) is another VGAM433 host target gene. KIAA1796 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1796, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1796 BINDING SITE, designated SEQ ID:43967, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20580] Another function of VGAM433 is therefore inhibition of

KIAA1796 (Accession XM\_166146). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1796. RNO2 (Accession NM\_033297) is another VGAM433 host target gene. RNO2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RNO2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNO2 BINDING SITE, designated SEQ ID:27127, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20581] Another function of VGAM433 is therefore inhibition of RNO2 (Accession NM\_033297). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNO2. Zinc Finger Protein 17 (HPF3, KOX 10) (ZNF17, Accession XM\_091895) is another VGAM433 host target gene. ZNF17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of ZNF17 BINDING SITE, designated SEQ ID:40066, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20582] Another function of VGAM433 is therefore inhibition of Zinc Finger Protein 17 (HPF3, KOX 10) (ZNF17, Accession XM\_091895). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF17. LOC145601 (Accession XM\_096816) is another VGAM433 host target gene. LOC145601 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145601, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145601 BINDING SITE, designated SEQ ID:40540, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20583] Another function of VGAM433 is therefore inhibition of LOC145601 (Accession XM\_096816). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC145601. LOC155340 (Accession XM\_055725) is another VGAM433 host target gene. LOC155340 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC155340, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155340 BINDING SITE, designated SEQ ID:36319, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20584] Another function of VGAM433 is therefore inhibition of LOC155340 (Accession XM\_055725). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155340. LOC256598 (Accession XM\_172816) is another VGAM433 host target gene. LOC256598 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256598, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256598 BINDING SITE, designated SEQ ID:46099, to the nucleotide sequence of VGAM433 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3144.

[20585] Another function of VGAM433 is therefore inhibition of LOC256598 (Accession XM\_172816). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256598. LOC257463 (Accession XM\_048605) is another VGAM433 host target gene. LOC257463 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257463, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257463 BINDING SITE, designated SEQ ID:35207, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20586] Another function of VGAM433 is therefore inhibition of LOC257463 (Accession XM\_048605). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257463. LOC83693 (Accession NM\_031463) is another VGAM433 host target gene. LOC83693 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC83693, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC83693 BINDING SITE, designated SEQ ID:25497, to the nucleotide sequence of VGAM433 RNA, herein designated VGAM RNA, also designated SEQ ID:3144.

[20587] Another function of VGAM433 is therefore inhibition of LOC83693 (Accession NM\_031463). Accordingly, utilities of VGAM433 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC83693. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 434 (VGAM434) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20588] VGAM434 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM434 was detected is described hereinabove with reference to Figs. 1–8.

[20589] VGAM434 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Sendai Virus. VGAM434

host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20590] VGAM434 gene encodes a VGAM434 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM434 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM434 precursor RNA is designated SEQ ID:420, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:420 is located at position 14005 relative to the genome of Sendai Virus.

[20591] VGAM434 precursor RNA folds onto itself, forming VGAM434 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20592] An enzyme complex designated DICER COMPLEX, `dices` the VGAM434 folded precursor RNA into VGAM434 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM434 RNA is designated SEQ ID:3145, and is provided hereinbelow with reference to the sequence listing part.

[20593] VGAM434 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM434 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM434 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20594] VGAM434 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM434 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM434 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM434 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM434 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20595] The complementary binding of VGAM434 RNA, herein designated VGAM RNA, to host target binding sites on VGAM434 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM434 host target RNA into VGAM434 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[20596] It is appreciated that VGAM434 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM434 host target genes. The mRNA of each one of this plurality of VGAM434 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM434 RNA, herein designated VGAM RNA, and which when bound by VGAM434 RNA causes inhibition of translation of respective one or more VGAM434 host target proteins.

[20597] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM434 gene, herein designated VGAM GENE, on one or more VGAM434 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20598] It is yet further appreciated that a function of VGAM434 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM434 include diagnosis, prevention and treatment of viral infection by Sendai Virus. Specific functions, and accordingly utilities, of VGAM434 correlate with, and may be deduced from, the identity of the host target genes which VGAM434 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20599] Nucleotide sequences of the VGAM434 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM434 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM434 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM434 are further described hereinbelow with reference to Table 1.

[20600] Nucleotide sequences of host target binding sites, such as



BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM434 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM434 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20601] As mentioned hereinabove with reference to Fig. 1, a function of VGAM434 gene, herein designated VGAM is inhibition of expression of VGAM434 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM434 correlate with, and may be deduced from, the identity of the target genes which VGAM434 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20602] KIAA0441 (Accession NM\_014797) is a VGAM434 host target gene. KIAA0441 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0441, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0441 BINDING SITE, designated SEQ ID:16712, to the nucleotide sequence of VGAM434 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3145.

[20603] A function of VGAM434 is therefore inhibition of KIAA0441 (Accession NM\_014797). Accordingly, utilities of VGAM434 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0441. KIAA0555 (Accession NM\_014790) is another VGAM434 host target gene. KIAA0555 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0555, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0555 BINDING SITE, designated SEQ ID:16679, to the nucleotide sequence of VGAM434 RNA, herein designated VGAM RNA, also designated SEQ ID:3145.

[20604] Another function of VGAM434 is therefore inhibition of KIAA0555 (Accession NM\_014790). Accordingly, utilities of VGAM434 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0555. Rab11-FIP2 (Accession NM\_014904) is another VGAM434 host target gene. Rab11-FIP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by Rab11-FIP2, corresponding

to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Rab11-FIP2 BINDING SITE, designated SEQ ID:17103, to the nucleotide sequence of VGAM434 RNA, herein designated VGAM RNA, also designated SEQ ID:3145.

[20605] Another function of VGAM434 is therefore inhibition of Rab11-FIP2 (Accession NM\_014904). Accordingly, utilities of VGAM434 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rab11-FIP2. LOC152992 (Accession XM\_087575) is another VGAM434 host target gene. LOC152992 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152992, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152992 BINDING SITE, designated SEQ ID:39348, to the nucleotide sequence of VGAM434 RNA, herein designated VGAM RNA, also designated SEQ ID:3145.

[20606] Another function of VGAM434 is therefore inhibition of LOC152992 (Accession XM\_087575). Accordingly, utilities of VGAM434 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC152992. LOC221830 (Accession XM\_166508) is another VGAM434 host target gene. LOC221830 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221830, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221830 BINDING SITE, designated SEQ ID:44438, to the nucleotide sequence of VGAM434 RNA, herein designated VGAM RNA, also designated SEQ ID:3145.

[20607] Another function of VGAM434 is therefore inhibition of LOC221830 (Accession XM\_166508). Accordingly, utilities of VGAM434 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221830. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 435 (VGAM435) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20608] VGAM435 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM435 was detected is described hereinabove with reference to Figs. 1–8.

[20609] VGAM435 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Sendai Virus. VGAM435 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20610] VGAM435 gene encodes a VGAM435 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM435 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM435 precursor RNA is designated SEQ ID:421, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:421 is located at position 11483 relative to the genome of Sendai Virus.

[20611] VGAM435 precursor RNA folds onto itself, forming VGAM435 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20612] An enzyme complex designated DICER COMPLEX, `dices` the VGAM435 folded precursor RNA into VGAM435 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 57%) nucleotide sequence of VGAM435 RNA is designated SEQ ID:3146, and is provided hereinbelow with reference to the sequence listing part.

[20613] VGAM435 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM435 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM435 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20614] VGAM435 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM435 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM435 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM435 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM435 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[20615] The complementary binding of VGAM435 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM435 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM435 host target RNA into VGAM435 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20616] It is appreciated that VGAM435 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM435 host target genes. The mRNA of each one of this plurality of VGAM435 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM435 RNA, herein designated VGAM RNA, and which when bound by VGAM435 RNA causes inhibition of translation of respective one or more VGAM435 host target proteins.

[20617] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM435 gene, herein designated VGAM GENE, on one or more VGAM435 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove



with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20618] It is yet further appreciated that a function of VGAM435 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of viral infection by Sendai Virus. Specific functions, and accordingly utilities, of VGAM435 correlate with, and may be deduced from, the identity of the host target genes which VGAM435 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20619] Nucleotide sequences of the VGAM435 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM435 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM435 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM435 are further described hereinbelow with reference to Table 1.

[20620] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM435 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM435 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20621] As mentioned hereinabove with reference to Fig. 1, a function of VGAM435 gene, herein designated VGAM is inhibition of expression of VGAM435 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM435 correlate with, and may be deduced from, the identity of the target genes which VGAM435 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20622] Rho GDP Dissociation Inhibitor (GDI) Alpha (ARHGDIA, Accession NM\_004309) is a VGAM435 host target gene. ARHGDIA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

ARHGDIA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGDIA BINDING SITE, designated SEQ ID:10514, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20623] A function of VGAM435 is therefore inhibition of Rho GDP Dissociation Inhibitor (GDI) Alpha (ARHGDIA, Accession NM\_004309), a gene which is a small guanine nucleotide exchange (GTP/GDP) factor. Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGDIA. The function of ARHGDIA has been established by previous studies. Ras-related homologs (ARHs), also called Rho genes, belong to the RAS gene superfamily encoding small guanine nucleotide exchange (GTP/GDP) factors. The ARH proteins may be kept in the inactive, GDP-bound state by interaction with GDP dissociation inhibitors (GDIAs). By screening a transformed amnion cell library with an ARHGDIB (OMIM Ref. No. 602843) cDNA, Leffers et al. (1993) isolated cDNAs encoding ARHGDIA. They found that ARHGDIA corresponded to a protein in the ker-

atinocyte 2-dimensional-gel protein database known as IEF (isoelectric focusing) 8118. By 2-dimensional gel electrophoresis, the predicted 204-amino acid protein had a pI of 4.74 and migrated at 29 kD. The amino acid sequences of human and bovine ARHGDIA are 97% identical. Leffers et al. (1993) found that the ARHGDIA gene contains 6 exons. Northern blot analysis revealed that ARHGDIA was expressed in all cell lines and tissues tested. Overexpression of ARHGDIB in mammalian cells caused them to 'round up' and disrupted the actin cytoskeleton, mimicking the phenotypic changes associated with inactivation of Rho proteins. Wagner et al. (1997) demonstrated by fluorescence in situ hybridization that the GDIA1 gene maps to 17q25.3. The assignment was confirmed by the use of a new somatic cell hybrid panel for 17q.

[20624] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20625] Leffers, H.; Nielsen, M. S.; Andersen, A. H.; Honore, B.; Madsen, P.; Vandekerckhove, J.; Celis, J. E. : Identification of two human rho GDP dissociation inhibitor proteins whose overexpression leads to disruption of the actin cytoskeleton. *Exp. Cell Res.* 209: 165–174, 1993. ; and

[20626] Wagner, T.; Tommerup, N.; Wirth, J.; Leffers, H.; Zimmer, J.; Back, E.; Weissenbach, J.; Scherer, G. : A somatic cell hybrid panel for distal 17q: GDIA1 maps to 17q25.3. Cytogenet. Cell.

[20627] Further studies establishing the function and utilities of ARHGDIA are found in John Hopkins OMIM database record ID 601925, and in cited publications numbered 5814–5815 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Corticotropin Releasing Hormone Receptor 1 (CRHR1, Accession NM\_004382) is another VGAM435 host target gene. CRHR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRHR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRHR1 BINDING SITE, designated SEQ ID:10607, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20628] Another function of VGAM435 is therefore inhibition of Corticotropin Releasing Hormone Receptor 1 (CRHR1, Accession NM\_004382), a gene which likely mediates physi-

ological and behavioral response to stress. Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRHR1. The function of CRHR1 has been established by previous studies. Grammatopoulos et al. (1998) studied the expression of CRHR1 in human myometrium. They used RT-PCR, fluorescence in situ hybridization, and immunofluorescence to identify and localize the 4 subtypes, 1-alpha, 1-beta, 2-alpha, and the variant C, of CRHR1. The CRHR1 subtypes in myometrium exhibited differential expression patterns; in human pregnant myometrium at term, all 4 receptor subtypes were expressed, whereas only the 1-alpha and 1-beta receptor subtypes were found in the nonpregnant myometrium. The authors concluded that CRHR1 acting via different receptor subtypes is able to exert different actions on the myometrium in the pregnant state compared to the nonpregnant state. Furthermore, in the pregnant human uterus, receptors were localized in both smooth muscle and fibroblasts, suggesting that CRHR1 expression plays an important modulatory role in myometrial and possibly in cervical function. Leproult et al. (2001) examined the effects of bright light on the profiles of hormones known to be af-

affected by sleep deprivation (TSH; OMIM Ref. No. 188540) or involved in behavioral activation (cortisol). The early morning transition from dim to bright light suppressed melatonin secretion, induced an immediate, greater than 50% elevation of cortisol levels, and limited the deterioration of alertness normally associated with overnight sleep deprivation. No effect was detected on TSH profiles. The authors concluded that these data unambiguously demonstrate an effect of light on the corticotropic axis that is dependent on time of day. Animal model experiments lend further support to the function of CRHR1. Sillaber et al. (2002) studied *Crhr1*  $-/-$  mice generated by Timpl et al. (1998). In homozygous mutant mice, stress leads to enhanced and progressively increasing alcohol intake. The effect of repeated stress on alcohol drinking behavior appeared with a delay and persisted throughout life. It was associated with an upregulation of the N-methyl-D-aspartate receptor subunit NR2B (OMIM Ref. No. 138252). Sillaber et al. (2002) concluded that alterations in the CRHR1 gene and adaptional changes in NR2B subunits may constitute a genetic risk factor for stress-induced alcohol drinking and alcoholism.

[20629] It is appreciated that the abovementioned animal model

for CRHR1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20630] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20631] Leproult, R.; Colecchia, E. F.; L'Hermite-Baleriaux, M.; Van Cauter, E. : Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels. J. Clin. Endocr. Metab. 86: 151–157, 2001. ; and

[20632] Sillaber, I.; Rammes, G.; Zimmermann, S.; Mahal, B.; Ziegler, W.; Wurst, W.; Holsboer, F.; Spanagel, R. : Enhanced and delayed stress-induced alcohol drinking in mice lacking fu.

[20633] Further studies establishing the function and utilities of CRHR1 are found in John Hopkins OMIM database record ID 122561, and in cited publications numbered 2034–1988, 264 and 2660–2663 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. C-myc Binding Protein (MYCBP, Accession NM\_012333) is another VGAM435 host target gene. MYCBP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MY-



CBP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYCBP BINDING SITE, designated SEQ ID:14723, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20634] Another function of VGAM435 is therefore inhibition of C-myc Binding Protein (MYCBP, Accession NM\_012333), a gene which binds c-Myc stimulating the activation of E-box-dependent transcription. Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYCBP. The function of MYCBP has been established by previous studies. To assess the molecular function of MYC-binding protein, Furusawa et al. (2001) performed a 2-hybrid screening of cDNAs encoding AMY1-binding proteins, with AMY1 as a bait using a human HeLa cDNA library. They found a clone encoding AKAP149 (AKAP1; 602449). AMY1 was found to bind in vitro and in vivo to the regulatory subunit II-binding region of AKAP1 and S-AKAP84, a splicing variant of AKAP149 expressed in the testis. AMY1 was expressed postmeiotically in the testis, as was also S-

AKAP84. AMY1 was localized in the mitochondria of HeLa and sperm in association with AKAP149 and S-AKAP84, respectively. These results suggested that AMY1 plays a role in spermatogenesis.

[20635] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20636] Furusawa, M.; Ohnishi, T.; Taira, T.; Iguchi-Ariga, S. M. M.; Ariga, H. : AMY-1, a c-Myc-binding protein, is localized in the mitochondria of sperm by association with S-AKAP84, an anchor protein of cAMP-dependent protein kinase. J. Biol. Chem. 276: 36647-36651, 2001. ; and

[20637] Taira, T.; Maeda, J.; Onishi, T.; Kitaura, H.; Yoshida, S.; Kato, H.; Ikeda, M.; Tamai, K.; Iguchi-Ariga, S. M. M.; Ariga, H. : AMY-1, a novel C-MYC binding protein that stimulates tra.

[20638] Further studies establishing the function and utilities of MYCBP are found in John Hopkins OMIM database record ID 606535, and in cited publications numbered 6466-6467 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Phosphatase 2A, Regulatory Subunit B' (PR 53) (PPP2R4, Accession XM\_026944) is another VGAM435 host target

gene. PPP2R4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2R4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R4 BINDING SITE, designated SEQ ID:30374, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20639] Another function of VGAM435 is therefore inhibition of Protein Phosphatase 2A, Regulatory Subunit B' (PR 53) (PPP2R4, Accession XM\_026944), a gene which is a regulatory subunit of protein phosphatase 2A. Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R4. The function of PPP2R4 has been established by previous studies. McCright et al. (1996) stated that PP2A contains a 36-kD catalytic C subunit (OMIM Ref. No. 176915) and a 65-kD structural/regulatory A subunit. Association of this dimeric core of PP2A with a third regulatory subunit (PR54, PR55, PR72, PR74, PR130, etc.) results in the formation of a specific trimeric holoenzyme. The PPP2R4 gene (which the authors symbolized PTPA) en-

codes a specific phosphotyrosyl phosphatase activator of the dimeric form of protein phosphatase 2A. Van Hoof et al. (1995) demonstrated that human PTPA is encoded by a single-copy gene composed of 10 exons and 9 introns with a total length of about 60 kb. The 5-prime flanking sequence of the transcription start site was analyzed for its potential as a promoter. This region lacks a TATA sequence in the appropriate position relative to the transcription start. However, this region is very GC-rich and contains four Sp1 sites (SP1; 189906) upstream of the transcription start site, a feature common to many TATA-less promoters. Based on homology with DNA-binding consensus sequences of transcription factors, Van Hoof et al. (1995) identified several additional putative transcription factor binding sites in the promoter region. Transfection experiments with a construct containing the PTPA promoter region inserted 5-prime of a luciferase reporter gene demonstrated that the 5-prime flanking sequence of the PTPA gene indeed has promoter activity that seems to be cell-line dependent. By fluorescence in situ hybridization, Van Hoof et al. (1995) mapped the PTPA gene to 9q34. Fluorescence in situ analysis of metaphase chromosomes of patients bearing the Philadelphia chromosome

indicated that PTPA is positioned centromeric of ABL1 (OMIM Ref. No. 189980) and probably is not involved in chronic myeloid leukemia.

[20640] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20641] McCright, B.; Rivers, A. M.; Audlin, S.; Virshup, D. M. : The B56 family of protein phosphatase 2A (PP2A) regulatory subunits encodes differentiation-induced phosphoproteins that target PP2A to both nucleus and cytoplasm. J. Biol. Chem. 271: 22081–22089, 1996. ; and

[20642] Van Hoof, C.; Aly, M. S.; Garcia, A.; Cayla, X.; Cassiman, J. J.; Merlevede, W.; Goris, J. : Structure and chromosomal localization of the human gene of the phosphotyrosyl phosphatase a.

[20643] Further studies establishing the function and utilities of PPP2R4 are found in John Hopkins OMIM database record ID 600756, and in cited publications numbered 8305–8306 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 5 Open Reading Frame 4 (C5orf4, Accession NM\_032385) is another VGAM435 host target gene. C5orf4 BINDING SITE is HOST TARGET binding site

found in the 3` untranslated region of mRNA encoded by C5orf4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C5orf4 BINDING SITE, designated SEQ ID:26179, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20644] Another function of VGAM435 is therefore inhibition of Chromosome 5 Open Reading Frame 4 (C5orf4, Accession NM\_032385). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C5orf4. Dynein, Axonemal, Light Polypeptide 4 (DNAL4, Accession NM\_005740) is another VGAM435 host target gene. DNAL4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DNAL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNAL4 BINDING SITE, designated SEQ ID:12306, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20645] Another function of VGAM435 is therefore inhibition of Dynein, Axonemal, Light Polypeptide 4 (DNAL4, Accession NM\_005740). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNAL4. Huntingtin-associated Protein Interacting Protein (duo) (HAIP, Accession NM\_003947) is another VGAM435 host target gene. HAIP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HAIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HAIP BINDING SITE, designated SEQ ID:10067, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20646] Another function of VGAM435 is therefore inhibition of Huntingtin-associated Protein Interacting Protein (duo) (HAIP, Accession NM\_003947). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HAIP. MGC15416 (Accession NM\_138418) is another VGAM435 host target gene. MGC15416 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of

mRNA encoded by MGC15416, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15416 BINDING SITE, designated SEQ ID:28787, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20647] Another function of VGAM435 is therefore inhibition of MGC15416 (Accession NM\_138418). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15416. Solute Carrier Family 25, (mitochondrial carrier), Member 18 (SLC25A18, Accession NM\_031481) is another VGAM435 host target gene. SLC25A18 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC25A18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC25A18 BINDING SITE, designated SEQ ID:25561, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20648] Another function of VGAM435 is therefore inhibition of



Solute Carrier Family 25, (mitochondrial carrier), Member 18 (SLC25A18, Accession NM\_031481). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC25A18. Solute Carrier Family 39 (zinc transporter), Member 3 (SLC39A3, Accession NM\_144564) is another VGAM435 host target gene. SLC39A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC39A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC39A3 BINDING SITE, designated SEQ ID:29356, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20649] Another function of VGAM435 is therefore inhibition of Solute Carrier Family 39 (zinc transporter), Member 3 (SLC39A3, Accession NM\_144564). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC39A3. LOC127534 (Accession XM\_060532) is another VGAM435 host target gene. LOC127534 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of

mRNA encoded by LOC127534, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127534 BINDING SITE, designated SEQ ID:37165, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20650] Another function of VGAM435 is therefore inhibition of LOC127534 (Accession XM\_060532). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127534. LOC132617 (Accession XM\_067939) is another VGAM435 host target gene. LOC132617 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC132617, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC132617 BINDING SITE, designated SEQ ID:37370, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20651] Another function of VGAM435 is therefore inhibition of LOC132617 (Accession XM\_067939). Accordingly, utilities

of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC132617. LOC91040 (Accession XM\_035641) is another VGAM435 host target gene. LOC91040 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91040 BINDING SITE, designated SEQ ID:32314, to the nucleotide sequence of VGAM435 RNA, herein designated VGAM RNA, also designated SEQ ID:3146.

[20652] Another function of VGAM435 is therefore inhibition of LOC91040 (Accession XM\_035641). Accordingly, utilities of VGAM435 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91040. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 436 (VGAM436) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20653] VGAM436 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM436 was detected is described hereinabove with reference to Figs. 1–8.

[20654] VGAM436 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Sendai Virus. VGAM436 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20655] VGAM436 gene encodes a VGAM436 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM436 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM436 precursor RNA is designated SEQ ID:422, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:422 is located at position 14126 relative to the genome of Sendai Virus.

[20656] VGAM436 precursor RNA folds onto itself, forming VGAM436 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20657] An enzyme complex designated DICER COMPLEX, `dices` the VGAM436 folded precursor RNA into VGAM436 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 77%) nucleotide sequence of VGAM436 RNA is designated SEQ ID:3147, and is provided hereinbelow with reference to the sequence listing part.

[20658] VGAM436 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM436 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM436 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20659] VGAM436 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM436 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM436 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM436 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM436 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20660] The complementary binding of VGAM436 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM436 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM436 host target RNA into VGAM436 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20661] It is appreciated that VGAM436 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM436 host target genes. The mRNA of each one of this plurality of VGAM436 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM436 RNA, herein designated VGAM RNA, and which when bound by VGAM436 RNA causes inhibition of translation of respective one or more VGAM436 host target proteins.

[20662] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM436 gene, herein designated VGAM GENE, on one or more VGAM436 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20663] It is yet further appreciated that a function of VGAM436 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM436 include diagnosis, prevention and treatment of viral infection by Sendai Virus. Specific functions, and accordingly utilities, of VGAM436 correlate with, and may be deduced from, the identity of the host target genes which VGAM436 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20664] Nucleotide sequences of the VGAM436 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the



5' duced 5' VGAM436 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM436 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM436 are further described hereinbelow with reference to Table 1.

[20665] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM436 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM436 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20666] As mentioned hereinabove with reference to Fig. 1, a function of VGAM436 gene, herein designated VGAM is inhibition of expression of VGAM436 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM436 correlate with, and may be deduced from, the identity of the target genes which VGAM436 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20667] PAG (Accession NM\_018440) is a VGAM436 host target gene. PAG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

PAG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAG BINDING SITE, designated SEQ ID:20508, to the nucleotide sequence of VGAM436 RNA, herein designated VGAM RNA, also designated SEQ ID:3147.

[20668] A function of VGAM436 is therefore inhibition of PAG (Accession NM\_018440). Accordingly, utilities of VGAM436 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAG. Chromosome 20 Open Reading Frame 50 (C20orf50, Accession XM\_046437) is another VGAM436 host target gene. C20orf50 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C20orf50, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf50 BINDING SITE, designated SEQ ID:34717, to the nucleotide sequence of VGAM436 RNA, herein designated VGAM RNA, also designated SEQ ID:3147.

[20669] Another function of VGAM436 is therefore inhibition of Chromosome 20 Open Reading Frame 50 (C20orf50, Ac-

cession XM\_046437). Accordingly, utilities of VGAM436 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf50.

KIAA1336 (Accession XM\_051306) is another VGAM436 host target gene. KIAA1336 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1336, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1336 BINDING SITE, designated SEQ ID:35802, to the nucleotide sequence of VGAM436 RNA, herein designated VGAM RNA, also designated SEQ ID:3147.

[20670] Another function of VGAM436 is therefore inhibition of KIAA1336 (Accession XM\_051306). Accordingly, utilities of VGAM436 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1336. PR Domain Containing 10 (PRDM10, Accession NM\_020228) is another VGAM436 host target gene. PRDM10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRDM10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of PRDM10 BINDING SITE, designated SEQ ID:21498, to the nucleotide sequence of VGAM436 RNA, herein designated VGAM RNA, also designated SEQ ID:3147.

[20671] Another function of VGAM436 is therefore inhibition of PR Domain Containing 10 (PRDM10, Accession NM\_020228). Accordingly, utilities of VGAM436 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRDM10. Tuftelin Interacting Protein 11 (TFIP11, Accession NM\_012143) is another VGAM436 host target gene. TFIP11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TFIP11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TFIP11 BINDING SITE, designated SEQ ID:14450, to the nucleotide sequence of VGAM436 RNA, herein designated VGAM RNA, also designated SEQ ID:3147.

[20672] Another function of VGAM436 is therefore inhibition of Tuftelin Interacting Protein 11 (TFIP11, Accession NM\_012143). Accordingly, utilities of VGAM436 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with TFIP11. LOC158364 (Accession XM\_088546) is another VGAM436 host target gene. LOC158364 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC158364, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158364 BINDING SITE, designated SEQ ID:39814, to the nucleotide sequence of VGAM436 RNA, herein designated VGAM RNA, also designated SEQ ID:3147.

[20673] Another function of VGAM436 is therefore inhibition of LOC158364 (Accession XM\_088546). Accordingly, utilities of VGAM436 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158364. LOC253613 (Accession XM\_171225) is another VGAM436 host target gene. LOC253613 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC253613, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC253613 BINDING SITE, designated SEQ ID:46010, to the nucleotide sequence of VGAM436 RNA, herein designated VGAM RNA, also designated SEQ ID:3147.

[20674] Another function of VGAM436 is therefore inhibition of LOC253613 (Accession XM\_171225). Accordingly, utilities of VGAM436 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253613. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 437 (VGAM437) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20675] VGAM437 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM437 was detected is described hereinabove with reference to Figs. 1–8.

[20676] VGAM437 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Bushy Stunt Virus. VGAM437 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20677] VGAM437 gene encodes a VGAM437 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM437 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM437 precursor RNA is designated SEQ ID:423, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:423 is located at position 3049 relative to the genome of Tomato Bushy Stunt Virus.

[20678] VGAM437 precursor RNA folds onto itself, forming VGAM437 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20679] An enzyme complex designated DICER COMPLEX, `dices` the VGAM437 folded precursor RNA into VGAM437 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM437 RNA is designated SEQ ID:3148, and is provided hereinbelow with reference to the sequence listing part.

[20680] VGAM437 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM437 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM437 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20681] VGAM437 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM437 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM437 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-



illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM437 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM437 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20682] The complementary binding of VGAM437 RNA, herein designated VGAM RNA, to host target binding sites on VGAM437 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM437 host target RNA into VGAM437 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20683] It is appreciated that VGAM437 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM437 host target genes. The mRNA of each one of this plurality of VGAM437 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM437 RNA, herein designated VGAM RNA, and which when bound by VGAM437 RNA causes inhibition of translation of respective one or more VGAM437 host target proteins.

[20684] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM437 gene, herein designated VGAM GENE, on one or more VGAM437 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[20685] It is yet further appreciated that a function of VGAM437 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM437 include diagnosis, prevention and treatment of viral infection by Tomato Bushy Stunt Virus. Specific functions, and accordingly utilities, of VGAM437 correlate with, and may be deduced from, the identity of the host target genes which VGAM437 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20686] Nucleotide sequences of the VGAM437 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM437 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM437 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM437 are further described hereinbelow with reference to Table 1.

[20687] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM437 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM437 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20688] As mentioned hereinabove with reference to Fig. 1, a function of VGAM437 gene, herein designated VGAM is inhibition of expression of VGAM437 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM437 correlate with, and may be deduced from, the identity of the target genes which VGAM437 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20689] Sulfotransferase Family, Cytosolic, 1C, Member 1 (SULT1C1, Accession NM\_001056) is a VGAM437 host target gene. SULT1C1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SULT1C1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SULT1C1 BINDING SITE, designated SEQ ID:6721, to the nucleotide sequence of VGAM437 RNA, herein designated VGAM RNA, also designated SEQ ID:3148.

[20690] A function of VGAM437 is therefore inhibition of Sulfo-transferase Family, Cytosolic, 1C, Member 1 (SULT1C1, Accession NM\_001056). Accordingly, utilities of VGAM437 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SULT1C1. HRIHFB2436 (Accession NM\_014345) is another VGAM437 host target gene. HRIHFB2436 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HRIHFB2436, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HRIHFB2436 BINDING SITE, designated SEQ ID:15667, to the nucleotide sequence of VGAM437 RNA, herein designated VGAM RNA, also designated SEQ ID:3148.

[20691] Another function of VGAM437 is therefore inhibition of HRIHFB2436 (Accession NM\_014345). Accordingly, utilities of VGAM437 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HRIHFB2436. LOC139065 (Accession XM\_066456) is another VGAM437 host target gene. LOC139065 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC139065, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC139065 BINDING SITE, designated SEQ ID:37327, to the nucleotide sequence of VGAM437 RNA, herein designated VGAM RNA, also designated SEQ ID:3148.

[20692] Another function of VGAM437 is therefore inhibition of LOC139065 (Accession XM\_066456). Accordingly, utilities of VGAM437 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC139065. LOC151584 (Accession XM\_098089) is another VGAM437 host target gene. LOC151584 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151584, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151584 BINDING SITE, designated SEQ ID:41375, to the nucleotide sequence of VGAM437 RNA, herein designated VGAM RNA, also designated SEQ ID:3148.

[20693] Another function of VGAM437 is therefore inhibition of LOC151584 (Accession XM\_098089). Accordingly, utilities of VGAM437 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC151584. LOC222166 (Accession XM\_168425) is another VGAM437 host target gene. LOC222166 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222166 BINDING SITE, designated SEQ ID:45155, to the nucleotide sequence of VGAM437 RNA, herein designated VGAM RNA, also designated SEQ ID:3148.

[20694] Another function of VGAM437 is therefore inhibition of LOC222166 (Accession XM\_168425). Accordingly, utilities of VGAM437 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222166. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 438 (VGAM438) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20695] VGAM438 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM438 was detected is described hereinabove with reference to Figs. 1–8.

[20696] VGAM438 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Bushy Stunt Virus. VGAM438 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20697] VGAM438 gene encodes a VGAM438 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM438 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM438 precursor RNA is designated SEQ ID:424, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:424 is located at position 3276 relative to the genome of Tomato Bushy Stunt Virus.

[20698] VGAM438 precursor RNA folds onto itself, forming VGAM438 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA



genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20699] An enzyme complex designated DICER COMPLEX, `dices` the VGAM438 folded precursor RNA into VGAM438 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 73%) nucleotide sequence of VGAM438 RNA is designated SEQ ID:3149, and is provided hereinbelow with reference to the sequence listing part.

[20700] VGAM438 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM438 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM438 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20701] VGAM438 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM438 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM438 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM438 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM438 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20702] The complementary binding of VGAM438 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM438 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM438 host target RNA into VGAM438 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20703] It is appreciated that VGAM438 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM438 host target genes. The mRNA of each one of this plurality of VGAM438 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM438 RNA, herein designated VGAM RNA, and which when bound by VGAM438 RNA causes inhibition of translation of respective one or more VGAM438 host target proteins.

[20704] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM438 gene, herein designated VGAM GENE, on one or more VGAM438 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20705] It is yet further appreciated that a function of VGAM438 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM438 include diagnosis, prevention and treatment of viral infection by Tomato Bushy Stunt Virus. Specific functions, and accordingly utilities, of VGAM438 correlate with, and may be deduced from, the identity of the host target genes which VGAM438 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20706] Nucleotide sequences of the VGAM438 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM438 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM438 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM438 are further described hereinbelow with reference to Table 1.

[20707] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM438 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM438 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20708] As mentioned hereinabove with reference to Fig. 1, a function of VGAM438 gene, herein designated VGAM is inhibition of expression of VGAM438 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM438 correlate with, and may be deduced from, the identity of the target genes which VGAM438 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20709] Alcohol Dehydrogenase 5 (class III), Chi Polypeptide (ADH5, Accession NM\_000671) is a VGAM438 host target gene. ADH5 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by ADH5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADH5 BINDING SITE, designated SEQ ID:6323, to the nucleotide sequence of VGAM438 RNA, herein designated VGAM RNA, also designated SEQ ID:3149.

[20710] A function of VGAM438 is therefore inhibition of Alcohol Dehydrogenase 5 (class III), Chi Polypeptide (ADH5, Accession NM\_000671), a gene which oxidizes ethanol and activated by fatty acids. It oxidizes ethanol very poorly. Accordingly, utilities of VGAM438 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADH5. The function of ADH5 has been established by previous studies. See 103720. Adinolfi et al. (1984) purified the chi isozyme of ADH (EC 1.1.1.1) from human liver and used it to raise immune sera. Its immunologic properties suggested that it has no structural similarity to either class I (ADH1, ADH2, ADH3) or class II (ADH4) isozymes. The chi isozyme was found in most human tissues including fetal specimens of 16 weeks gestational age and showed a preference for long chain primary alcohols with a double bond in the beta position. Adinolfi

et al. (1984) concluded that the locus, designated ADH5, has a separate evolutionary origin from other ADH genes. (The class I ADH isozymes are virtually indistinguishable immunologically; the genes that determine them presumably originated by gene duplication.) Class III or chi ADH has specificity for complex alcohols of high molecular weight such as cinnamyl alcohol. Beisswenger et al. (1985) showed that ADH-chi is the only ADH isozyme in brain. It oxidizes ethanol very poorly; its function in brain is unknown. Since its gene is expressed constitutively in somatic cell hybrids, Carlock et al. (1985) could assign the locus to chromosome 4, specifically 4q21-q25, by analysis of gene products in starch gel electrophoresis. Smith (1986) gave the regional assignment as 4q21-q24. Goldman et al. (1989) isolated and sequenced a full-length cDNA for the class III alcohol dehydrogenase ADH5. By analysis of human/hamster hybrid cell lines, ADH5 was mapped to chromosome 4 where other ADH genes have been located, including class I genes and a class II gene, all of which metabolize ethanol, and the unusual class III ADH, which does not. Analysis of mouse/hamster hybrid cell lines showed that the corresponding gene maps to mouse chromosome 3, which carries the other murine

ADH genes. The sequence of ADH5 indicated that it is about equidistant between class I and class II ADHs. In contrast to other ADHs whose expression is more restricted, class III ADH was found to be expressed ubiquitously in human and rodent tissues. Giri et al. (1989) also mapped the gene to mouse chromosome 3. Matsuo and Yokoyama (1990) demonstrated a processed pseudogene derived from the ADH5 gene. Engeland et al. (1993) reported the kinetic characterization of human class III ADH altered at position 115 to asp and to ala by in vitro mutagenesis. The results indicated that the arg115 residue is a component of the binding site for activating fatty acids and is critical for the binding of S-hydroxymethylglutathione in glutathione-dependent formaldehyde dehydrogenase activity.

[20711] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20712] Matsuo, Y.; Yokoyama, S. : Cloning and sequencing of a processed pseudogene derived from a human class III alcohol dehydrogenase gene. Am. J. Hum. Genet. 46: 85-91, 1990. ; and

[20713] Engeland, K.; Hoog, J.-O.; Holmquist, B.; Estonius, M.;



Jornvall, H.; Vallee, B. L. : Mutation of arg-115 of human class III alcohol dehydrogenase: a binding site required for formaldehy.

[20714] Further studies establishing the function and utilities of ADH5 are found in John Hopkins OMIM database record ID 103710, and in cited publications numbered 811-818 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Endoglin (Osler-Rendu-Weber syndrome 1) (ENG, Accession NM\_000118) is another VGAM438 host target gene. ENG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ENG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ENG BINDING SITE, designated SEQ ID:5590, to the nucleotide sequence of VGAM438 RNA, herein designated VGAM RNA, also designated SEQ ID:3149.

[20715] Another function of VGAM438 is therefore inhibition of Endoglin (Osler-Rendu-Weber syndrome 1) (ENG, Accession NM\_000118). Accordingly, utilities of VGAM438 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ENG. Protein Phos-

phatase 4, Regulatory Subunit 2 (PPP4R2, Accession NM\_019853) is another VGAM438 host target gene. PPP4R2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PPP4R2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP4R2 BINDING SITE, designated SEQ ID:21256, to the nucleotide sequence of VGAM438 RNA, herein designated VGAM RNA, also designated SEQ ID:3149.

[20716] Another function of VGAM438 is therefore inhibition of Protein Phosphatase 4, Regulatory Subunit 2 (PPP4R2, Accession NM\_019853). Accordingly, utilities of VGAM438 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP4R2.

LOC200854 (Accession XM\_113396) is another VGAM438 host target gene. LOC200854 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC200854, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200854 BINDING

SITE, designated SEQ ID:42252, to the nucleotide sequence of VGAM438 RNA, herein designated VGAM RNA, also designated SEQ ID:3149.

[20717] Another function of VGAM438 is therefore inhibition of LOC200854 (Accession XM\_113396). Accordingly, utilities of VGAM438 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200854. LOC253187 (Accession XM\_173139) is another VGAM438 host target gene. LOC253187 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253187, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253187 BINDING SITE, designated SEQ ID:46392, to the nucleotide sequence of VGAM438 RNA, herein designated VGAM RNA, also designated SEQ ID:3149.

[20718] Another function of VGAM438 is therefore inhibition of LOC253187 (Accession XM\_173139). Accordingly, utilities of VGAM438 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253187. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 439 (VGAM439) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20719] VGAM439 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM439 was detected is described hereinabove with reference to Figs. 1–8.

[20720] VGAM439 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Bushy Stunt Virus. VGAM439 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20721] VGAM439 gene encodes a VGAM439 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM439 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM439 precursor RNA is designated SEQ ID:425, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:425 is located at position 2898 relative to the genome of Tomato

## Bushy Stunt Virus.

[20722] VGAM439 precursor RNA folds onto itself, forming VGAM439 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20723] An enzyme complex designated DICER COMPLEX, `dices` the VGAM439 folded precursor RNA into VGAM439 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 61%) nucleotide sequence of VGAM439 RNA is designated SEQ ID:3150, and is provided hereinbelow with reference to the sequence listing part.

[20724] VGAM439 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM439 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM439 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20725] VGAM439 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM439 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM439 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM439 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM439 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[20726] The complementary binding of VGAM439 RNA, herein designated VGAM RNA, to host target binding sites on VGAM439 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM439 host target RNA into VGAM439 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20727] It is appreciated that VGAM439 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM439 host target genes. The mRNA of each one of this plurality of VGAM439 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM439 RNA, herein designated VGAM RNA, and which when bound by VGAM439 RNA causes inhibition of translation of respective one or more VGAM439 host target proteins.

[20728] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM439 gene, herein designated VGAM GENE, on one or more VGAM439 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20729] It is yet further appreciated that a function of VGAM439 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of viral infection by Tomato Bushy Stunt Virus. Specific functions, and accordingly utilities, of VGAM439



correlate with, and may be deduced from, the identity of the host target genes which VGAM439 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20730] Nucleotide sequences of the VGAM439 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM439 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM439 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM439 are further described hereinbelow with reference to Table 1.

[20731] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM439 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM439 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20732] As mentioned hereinabove with reference to Fig. 1, a function of VGAM439 gene, herein designated VGAM is inhibition of expression of VGAM439 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM439 correlate with, and may be deduced

from, the identity of the target genes which VGAM439 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20733] GAC1 (Accession NM\_006338) is a VGAM439 host target gene. GAC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAC1 BINDING SITE, designated SEQ ID:13039, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20734] A function of VGAM439 is therefore inhibition of GAC1 (Accession NM\_006338). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAC1. GRAF (Accession NM\_015071) is another VGAM439 host target gene. GRAF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRAF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRAF BINDING SITE, designated SEQ

ID:17446, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20735] Another function of VGAM439 is therefore inhibition of GRAF (Accession NM\_015071), a gene which is a GTPase activating protein for p21-rac. Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRAF. The function of GRAF and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM430. Nuclear Factor I/B (NFIB, Accession NM\_005596) is another VGAM439 host target gene. NFIB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NFIB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFIB BINDING SITE, designated SEQ ID:12121, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20736] Another function of VGAM439 is therefore inhibition of Nuclear Factor I/B (NFIB, Accession NM\_005596), a gene

which recognizes and binds the palindromic sequence 5'-ttggcnnnnngccaa-3' present in viral and cellular promoters. Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NFIB. The function of NFIB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM100.SMG1 (Accession NM\_015092) is another VGAM439 host target gene. SMG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SMG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMG1 BINDING SITE, designated SEQ ID:17478, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20737] Another function of VGAM439 is therefore inhibition of SMG1 (Accession NM\_015092), a gene which acts as the target for the cell-cycle arrest and immunosuppressive effects. Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMG1. The function of SMG1 and its

association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM419. Bromodomain Containing 4 (BRD4, Accession NM\_058243) is another VGAM439 host target gene. BRD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BRD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BRD4 BINDING SITE, designated SEQ ID:27775, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20738] Another function of VGAM439 is therefore inhibition of Bromodomain Containing 4 (BRD4, Accession NM\_058243). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BRD4. Aspartyl-tRNA Synthetase (DARS, Accession NM\_001349) is another VGAM439 host target gene. DARS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DARS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DARS BINDING SITE, designated SEQ ID:7030, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20739] Another function of VGAM439 is therefore inhibition of Aspartyl-tRNA Synthetase (DARS, Accession NM\_001349). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DARS. FLJ14641 (Accession NM\_032817) is another VGAM439 host target gene. FLJ14641 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14641, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14641 BINDING SITE, designated SEQ ID:26590, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20740] Another function of VGAM439 is therefore inhibition of FLJ14641 (Accession NM\_032817). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14641.

KIAA1056 (Accession NM\_014894) is another VGAM439 host target gene. KIAA1056 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1056 BINDING SITE, designated SEQ ID:17049, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20741] Another function of VGAM439 is therefore inhibition of KIAA1056 (Accession NM\_014894). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1056. KIAA1854 (Accession XM\_049884) is another VGAM439 host target gene. KIAA1854 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1854, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1854 BINDING SITE, designated SEQ ID:35520, to the nucleotide sequence of VGAM439 RNA, herein designated

VGAM RNA, also designated SEQ ID:3150.

[20742] Another function of VGAM439 is therefore inhibition of KIAA1854 (Accession XM\_049884). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1854. MGC15631 (Accession NM\_032753) is another VGAM439 host target gene. MGC15631 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC15631, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15631 BINDING SITE, designated SEQ ID:26488, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20743] Another function of VGAM439 is therefore inhibition of MGC15631 (Accession NM\_032753). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15631. SAM Domain and HD Domain 1 (SAMHD1, Accession XM\_028704) is another VGAM439 host target gene. SAMHD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by



SAMHD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SAMHD1 BINDING SITE, designated SEQ ID:30736, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20744] Another function of VGAM439 is therefore inhibition of SAM Domain and HD Domain 1 (SAMHD1, Accession XM\_028704). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SAMHD1. Williams–Beuren Syndrome Chromosome Region 23 (WBSCR23, Accession NM\_025042) is another VGAM439 host target gene. WBSCR23 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by WBSCR23, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WBSCR23 BINDING SITE, designated SEQ ID:24639, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20745] Another function of VGAM439 is therefore inhibition of Williams–Beuren Syndrome Chromosome Region 23 (WBSCR23, Accession NM\_025042). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WB–SCR23. LOC162333 (Accession XM\_102591) is another VGAM439 host target gene. LOC162333 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC162333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162333 BINDING SITE, designated SEQ ID:42136, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20746] Another function of VGAM439 is therefore inhibition of LOC162333 (Accession XM\_102591). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162333. LOC220003 (Accession XM\_166230) is another VGAM439 host target gene. LOC220003 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC220003, cor–

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220003 BINDING SITE, designated SEQ ID:44051, to the nucleotide sequence of VGAM439 RNA, herein designated VGAM RNA, also designated SEQ ID:3150.

[20747] Another function of VGAM439 is therefore inhibition of LOC220003 (Accession XM\_166230). Accordingly, utilities of VGAM439 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220003. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 440 (VGAM440) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20748] VGAM440 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM440 was detected is described hereinabove with reference to Figs. 1–8.

[20749] VGAM440 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM440 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20750] VGAM440 gene encodes a VGAM440 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM440 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM440 precursor RNA is designated SEQ ID:426, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:426 is located at position 22113 relative to the genome of Vaccinia Virus.

[20751] VGAM440 precursor RNA folds onto itself, forming VGAM440 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20752] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM440 folded precursor RNA into VGAM440 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM440 RNA is designated SEQ ID:3151, and is provided hereinbelow with reference to the sequence listing part.

[20753] VGAM440 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM440 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM440 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20754] VGAM440 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM440 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM440 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM440 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM440 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20755] The complementary binding of VGAM440 RNA, herein designated VGAM RNA, to host target binding sites on VGAM440 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM440 host target RNA into VGAM440 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20756] It is appreciated that VGAM440 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM440 host target genes. The mRNA of each one of this plurality of VGAM440 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM440 RNA, herein designated VGAM RNA, and which when bound by VGAM440 RNA causes inhibition of translation of respective one or more VGAM440 host target proteins.

[20757] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM440 gene, herein designated VGAM GENE, on one or more VGAM440 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20758] It is yet further appreciated that a function of VGAM440 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM440 correlate with, and may be deduced from, the identity of the host target genes which VGAM440 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20759] Nucleotide sequences of the VGAM440 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM440 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM440 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM440 are further described hereinbelow with reference to Table 1.



[20760] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM440 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM440 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20761] As mentioned hereinabove with reference to Fig. 1, a function of VGAM440 gene, herein designated VGAM is inhibition of expression of VGAM440 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM440 correlate with, and may be deduced from, the identity of the target genes which VGAM440 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20762] Autocrine Motility Factor Receptor (AMFR, Accession NM\_138958) is a VGAM440 host target gene. AMFR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AMFR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AMFR BINDING SITE, designated SEQ ID:29066, to the nu-

cleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20763] A function of VGAM440 is therefore inhibition of Autocrine Motility Factor Receptor (AMFR, Accession NM\_138958), a gene which acts to stimulate migration of fibrosarcoma cells. Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AMFR. The function of AMFR has been established by previous studies. Autocrine motility factor (AMF; 172400) is a protein secreted by tumor cells that stimulates tumor motility. Its receptor is a 78-kD glycoprotein (gp78). Watanabe et al. (1991) cloned the AMFR cDNA. The gene encodes a 323-amino acid polypeptide that has a single transmembrane domain and several putative glycosylation sites. The protein sequence has some homology to human tumor protein p53 (OMIM Ref. No. 191170). Hirono et al. (1996) used immunohistochemistry to examine the expression of AMFR in gastric cancer specimens. The level of expression was associated with the pathologic stage and grade of tumor penetration. Positive AMFR expression was significantly associated with poor prognosis.

[20764] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [20765] Hirono, Y.; Fushida, S.; Yonemura, Y.; Yamamoto, H.; Watanabe, H.; Raz, A. : Expression of autocrine motility factor receptor correlates with disease progression in human gastric cancer. Brit. J. Cancer 74: 2003–2007, 1996. ; and
- [20766] Watanabe, H.; Carmi, P.; Hogan, V.; Raz, T.; Silletti, S.; Nabi, I. R.; Raz, A. : Purification of human tumor cell autocrine motility factor and molecular cloning of its receptor. J. Bio.
- [20767] Further studies establishing the function and utilities of AMFR are found in John Hopkins OMIM database record ID 603243, and in cited publications numbered 1079–1082 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromogranin A (parathyroid secretory protein 1) (CHGA, Accession NM\_001275) is another VGAM440 host target gene. CHGA BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CHGA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

CHGA BINDING SITE, designated SEQ ID:6939, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20768] Another function of VGAM440 is therefore inhibition of Chromogranin A (parathyroid secretory protein 1) (CHGA, Accession NM\_001275), a gene which regulates dense-core secretory granule biogenesis and hormone sequestration. Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHGA. The function of CHGA has been established by previous studies. Kim et al. (2001) presented evidence that regulation of dense-core secretory granule biogenesis and hormone secretion in endocrine cells is dependent on CGA. Downregulation of CGA expression in a neuroendocrine cell line, PC12, by antisense RNAs led to profound loss of dense-core secretory granules, impairment of regulated secretion of a transfected prohormone, and reduction of secretory granule proteins. Transfection of bovine Cga into a CGA-deficient PC12 clone rescued the regulated secretory phenotype. Stable transfection of CGA into a CGA-deficient pituitary cell line, 6T3, which lacks a regulated secretory pathway, restored regulated secretion. Overexpression of

CGA induced dense-core granules, immunoreactive for CGA, in nonendocrine fibroblast CV-1 cells. Kim et al. (2001) concluded that CGA is an 'on/off' switch that alone is sufficient to drive dense-core secretory granule biogenesis and hormone sequestration in endocrine cells.

Granberg et al. (1999) measured CgA in 36 patients with type I multiple endocrine neoplasia (MEN1; 131100), of whom 9 lacked pancreatic involvement, 20 had biochemical evidence of pancreatic endocrine tumors, and 7 displayed radiologically detectable pancreatic tumors. CgA was also analyzed in 25 patients with sporadic pancreatic endocrine tumors, 39 subjects with inflammatory bowel disease, 7 patients harboring nonendocrine pancreatic disease, and 19 healthy controls. Of the MEN1 patients without pancreatic involvement, 4 of 9 (44%) had elevated CgA. Furthermore, 60% with biochemically unequivocal tumors and all with a radiologically visible tumor showed elevations. All 25 patients with sporadic pancreatic endocrine tumors had increased CgA, as did 28% of patients with inflammatory bowel disease and 57% with nonendocrine pancreatic disease. Granberg et al. (1999) concluded that nonendocrine diseases can cause elevations of CgA, and its spontaneous variation can be considerable.

While plasma CgA is the most sensitive of the basal markers for neuroendocrine tumors, the authors felt that it could not replace other established measures when screening for early pancreatic involvement in MEN1.

[20769] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20770] Granberg, D.; Stridsberg, M.; Seensalu, R.; Eriksson, B.; Lundqvist, G.; Oberg, K.; Skogseid, B. : Plasma chromogranin A in patients with multiple endocrine neoplasia type 1. J. Clin. Endocr. Metab. 84: 2712–2717, 1999. ; and

[20771] Kim, T.; Tao-Cheng, J.-H.; Eiden, L. E.; Loh, Y. P. : Chromogranin A, an 'on/off' switch controlling dense-core secretory granule biogenesis. Cell 106: 499–509, 2001.

[20772] Further studies establishing the function and utilities of CHGA are found in John Hopkins OMIM database record ID 118910, and in cited publications numbered 12299–1230 and 790–259 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ10842 (Accession NM\_018238) is another VGAM440 host target gene. FLJ10842 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10842, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10842 BINDING SITE, designated SEQ ID:20187, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20773] Another function of VGAM440 is therefore inhibition of FLJ10842 (Accession NM\_018238). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10842. FLJ22969 (Accession XM\_044006) is another VGAM440 host target gene. FLJ22969 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22969, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22969 BINDING SITE, designated SEQ ID:34067, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20774] Another function of VGAM440 is therefore inhibition of FLJ22969 (Accession XM\_044006). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ22969. FLJ23510 (Accession NM\_024720) is another VGAM440 host target gene. FLJ23510 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ23510, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23510 BINDING SITE, designated SEQ ID:24052, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20775] Another function of VGAM440 is therefore inhibition of FLJ23510 (Accession NM\_024720). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23510. FLJ23519 (Accession NM\_032240) is another VGAM440 host target gene. FLJ23519 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23519 BINDING SITE, designated SEQ ID:25971, to the nucleotide sequence of



VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20776] Another function of VGAM440 is therefore inhibition of FLJ23519 (Accession NM\_032240). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23519. KIAA0961 (Accession NM\_014898) is another VGAM440 host target gene. KIAA0961 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0961, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0961 BINDING SITE, designated SEQ ID:17071, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20777] Another function of VGAM440 is therefore inhibition of KIAA0961 (Accession NM\_014898). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0961. KIAA1265 (Accession XM\_047707) is another VGAM440 host target gene. KIAA1265 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1265, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1265 BINDING SITE, designated SEQ ID:35034, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20778] Another function of VGAM440 is therefore inhibition of KIAA1265 (Accession XM\_047707). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1265. Solute Carrier Family 6 (neurotransmitter transporter), Member 14 (SLC6A14, Accession NM\_007231) is another VGAM440 host target gene. SLC6A14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC6A14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC6A14 BINDING SITE, designated SEQ ID:14100, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20779] Another function of VGAM440 is therefore inhibition of Solute Carrier Family 6 (neurotransmitter transporter), Member 14 (SLC6A14, Accession NM\_007231). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC6A14. Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession XM\_053740) is another VGAM440 host target gene. TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TP53INP1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2, designated SEQ ID:36114 and SEQ ID:27103 respectively, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20780] Another function of VGAM440 is therefore inhibition of Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession XM\_053740). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TP53INP1.

LOC147429 (Accession XM\_085793) is another VGAM440 host target gene. LOC147429 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147429, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147429 BINDING SITE, designated SEQ ID:38335, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20781] Another function of VGAM440 is therefore inhibition of LOC147429 (Accession XM\_085793). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147429. LOC154007 (Accession XM\_087824) is another VGAM440 host target gene. LOC154007 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154007, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154007 BINDING SITE, designated SEQ ID:39455, to the nucleotide sequence of VGAM440 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3151.

[20782] Another function of VGAM440 is therefore inhibition of LOC154007 (Accession XM\_087824). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154007. LOC196337 (Accession XM\_113696) is another VGAM440 host target gene. LOC196337 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196337 BINDING SITE, designated SEQ ID:42358, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20783] Another function of VGAM440 is therefore inhibition of LOC196337 (Accession XM\_113696). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196337. LOC200197 (Accession XM\_114148) is another VGAM440 host target gene. LOC200197 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200197, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200197 BINDING SITE, designated SEQ ID:42730, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20784] Another function of VGAM440 is therefore inhibition of LOC200197 (Accession XM\_114148). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200197. LOC200681 (Accession XM\_117260) is another VGAM440 host target gene. LOC200681 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200681, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200681 BINDING SITE, designated SEQ ID:43341, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20785] Another function of VGAM440 is therefore inhibition of LOC200681 (Accession XM\_117260). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC200681. LOC221583 (Accession XM\_166396) is another VGAM440 host target gene. LOC221583 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221583, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221583 BINDING SITE, designated SEQ ID:44245, to the nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20786] Another function of VGAM440 is therefore inhibition of LOC221583 (Accession XM\_166396). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221583. LOC51301 (Accession NM\_016591) is another VGAM440 host target gene. LOC51301 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC51301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51301 BINDING SITE, designated SEQ ID:18670, to the

nucleotide sequence of VGAM440 RNA, herein designated VGAM RNA, also designated SEQ ID:3151.

[20787] Another function of VGAM440 is therefore inhibition of LOC51301 (Accession NM\_016591). Accordingly, utilities of VGAM440 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51301. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 441 (VGAM441) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20788] VGAM441 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM441 was detected is described hereinabove with reference to Figs. 1–8.

[20789] VGAM441 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM441 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20790] VGAM441 gene encodes a VGAM441 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM441 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM441 precursor RNA is designated SEQ ID:427, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:427 is located at position 78448 relative to the genome of Vaccinia Virus.

[20791] VGAM441 precursor RNA folds onto itself, forming VGAM441 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20792] An enzyme complex designated DICER COMPLEX, `dices` the VGAM441 folded precursor RNA into VGAM441 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 92%) nucleotide sequence of VGAM441 RNA is designated SEQ ID:3152, and is provided hereinbelow with reference to the sequence listing part.

[20793] VGAM441 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM441 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM441 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20794] VGAM441 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM441 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM441 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM441 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM441 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20795] The complementary binding of VGAM441 RNA, herein designated VGAM RNA, to host target binding sites on VGAM441 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM441 host target RNA into VGAM441 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20796] It is appreciated that VGAM441 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM441 host target genes. The mRNA of each one of this plurality of VGAM441 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM441 RNA, herein designated VGAM RNA, and which when bound by VGAM441 RNA causes inhibition of translation of respective one or more VGAM441 host target proteins.

[20797] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM441 gene, herein designated VGAM GENE, on one or more VGAM441 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[20798] It is yet further appreciated that a function of VGAM441 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM441 correlate with, and may be deduced from, the identity of the host target genes which VGAM441 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[20799] Nucleotide sequences of the VGAM441 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM441 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM441 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM441 are further described hereinbelow with reference to Table 1.

[20800] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM441 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM441 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20801] As mentioned hereinabove with reference to Fig. 1, a function of VGAM441 gene, herein designated VGAM is inhibition of expression of VGAM441 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM441 correlate with, and may be deduced from, the identity of the target genes which VGAM441 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20802] Cyclin T2 (CCNT2, Accession NM\_058241) is a VGAM441 host target gene. CCNT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CCNT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CCNT2 BINDING SITE, designated SEQ ID:27770, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20803] A function of VGAM441 is therefore inhibition of Cyclin T2 (CCNT2, Accession NM\_058241), a gene which is a regu-

latory subunit of the cyclin-dependent kinase pair (cdk9/cyclin t) complex. Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CCNT2. The function of CCNT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM159. Endothelin Receptor Type A (EDNRA, Accession XM\_034331) is another VGAM441 host target gene. EDNRA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EDNRA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EDNRA BINDING SITE, designated SEQ ID:32056, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20804] Another function of VGAM441 is therefore inhibition of Endothelin Receptor Type A (EDNRA, Accession XM\_034331), a gene which binds endothelins, and induces intracellular calcium flux and arachidonic acid accumulation. Accordingly, utilities of VGAM441 include di-

agnosis, prevention and treatment of diseases and clinical conditions associated with EDNRA. The function of EDNRA has been established by previous studies. See 131244.

The endothelin receptor with highest affinity for ET1 (OMIM Ref. No. 131240) has been called ETA. Cyr et al. (1991) isolated a cDNA clone of a human endothelin receptor from a placental cDNA library. The deduced amino acid sequence was 94% identical to the bovine endothelin ETA receptor and was judged to represent the human homolog. They assigned the ETRA gene to chromosome 4 by analysis of its segregation pattern in rodent/human hybrids. Hosoda et al. (1992) isolated and characterized the gene for the human endothelin-A receptor. Southern blot analyses demonstrated that it is present in single copy. The gene spans more than 40 kb and contains 8 exons and 7 introns. The transcription start site, determined by primer extension experiments, was 502 bp upstream of the methionine initiation codon. Using human/rodent somatic hybrid cell DNAs, Hosoda et al. (1992) also assigned the gene to chromosome 4. Northern blot analyses demonstrated a 4.3-kb mRNA in a wide variety of human tissues with the highest level in the aorta and a substantial level in cultured human mesangial cells. Endothelin-1



inhibits active Na–K transport by as much as 50% in the renal tubule and other tissues (Zeidel et al., 1989). Okafor and Delamere (2001) noted that the presence of low levels of ET1 in aqueous humor combined with the potential for release of ET1 from ciliary processes suggested that the crystalline lens could be exposed to ET1 in vivo. They studied the influence of ET1 on active Na–K transport in the porcine lens. Their results suggested that ET1 inhibited active lens Na–K transport by activating EDNRA and EDNRB. Activation of the ET receptors also caused an increase in cytoplasmic calcium concentration in cultured lens epithelial cells. Both responses to ET1 appear to have a tyrosine kinase step.

[20805] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20806] Hosoda, K.; Nakao, K.; Tamura, N.; Arai, H.; Ogawa, Y.; Suga, S.; Nakanishi, S.; Imura, H. : Organization, structure, chromosomal assignment, and expression of the gene encoding the human endothelin–A receptor. *J. Biol. Chem.* 267: 18797–18804, 1992. ; and

[20807] Okafor, M. C.; Delamere, N. A. : The inhibitory influence of endothelin on active sodium–potassium transport in

porcine lens. Invest. Ophthal. Vis. Sci. 42: 1018–1023, 2001.

[20808] Further studies establishing the function and utilities of EDNRA are found in John Hopkins OMIM database record ID 131243, and in cited publications numbered 12215–4038, 2278, 228 and 4039 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Growth Factor Receptor–bound Protein 10 (GRB10, Accession NM\_005311) is another VGAM441 host target gene. GRB10 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GRB10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRB10 BINDING SITE, designated SEQ ID:11785, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20809] Another function of VGAM441 is therefore inhibition of Growth Factor Receptor–bound Protein 10 (GRB10, Accession NM\_005311), a gene which plays a functional role in insulin and IGF–I signaling. Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with GRB10. The function of GRB10 has been established by previous studies. Src homology region 2 (SH2) domain proteins bind to autophosphorylated growth factor receptors after activation of the receptors by ligand. By screening an NIH 3T3 library with the epidermal growth factor receptor (EGFR; 131550) by use of the CORT technique (Skolnik et al., 1991), Ooi et al. (1995) cloned and characterized mouse Grb10. Grb10 undergoes serine but not tyrosine phosphorylation after EGF treatment and binds poorly to the EGFR, suggesting that another protein binds the EGFR in vivo. Ooi et al. (1995) mapped the mouse Grb10 gene to chromosome 11. By using the yeast 2-hybrid system to identify proteins that interact with the cytoplasmic tyrosine kinase domain of the insulin receptor (INSR; 147670), Liu and Roth (1995) isolated a GRB10 cDNA from HeLa cells. The cDNA, called GRB-IR by them, encodes a predicted 548-amino acid protein containing an SH2 domain and an incomplete pleckstrin-homology (PH) domain. RT-PCR showed that the GRB10 gene is alternatively spliced, producing transcripts that encode proteins either with or without a 46-amino acid stretch that contains part of the PH domain. The SH2 and PH domains of the human GRB10

protein are 99% and 84% identical, respectively, to those of mouse Grb10. Northern blot analysis showed that the GRB10 gene is expressed as 2.2-, 5.0-, and 6.5-kb transcripts, predominantly in skeletal muscle and pancreas. Western blot analysis of HeLa cell lysates detected 50-, 65-, and 68-kD proteins. GRB10 binds with high affinity to autophosphorylated INSR in vitro. After treatment of cells with insulin (INS; 176730), GRB10 forms complexes with INSR. The formation of this complex inhibits the insulin-induced increase in phosphorylation of IRS1 (OMIM Ref. No. 147545) and a 60-kD GTPase-activating protein (GAP)-associated protein, suggesting that GRB10 inhibits or redirects the INSR signaling pathway.

[20810] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20811] Liu, F.; Roth, R. A. : Grb-IR: a SH2-domain-containing protein that binds to the insulin receptor and inhibits its function. Proc. Nat. Acad. Sci. 92: 10287-10291, 1995. ; and

[20812] Ooi, J.; Yajnik, V.; Immanuel, D.; Gordon, M.; Moskow, J. J.; Buchberg, A. M.; Margolis, B. : The cloning of Grb10 reveals a new family of SH2 domain proteins. Oncogene 10:

1621–1630, 1.

[20813] Further studies establishing the function and utilities of GRB10 are found in John Hopkins OMIM database record ID 601523, and in cited publications numbered 6526, 6527–6528, 1809, 6529–6530, 1810–181 and 6531 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. 5–hydroxytryptamine (serotonin) Receptor 4 (HTR4, Accession NM\_000870) is another VGAM441 host target gene. HTR4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HTR4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HTR4 BINDING SITE, designated SEQ ID:6540, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20814] Another function of VGAM441 is therefore inhibition of 5–hydroxytryptamine (serotonin) Receptor 4 (HTR4, Accession NM\_000870), a gene which mediates calcium channel currents. Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTR4. The function of

HTR4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM65. Jagged 1 (Alagille syndrome) (JAG1, Accession NM\_000214) is another VGAM441 host target gene. JAG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JAG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JAG1 BINDING SITE, designated SEQ ID:5712, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20815] Another function of VGAM441 is therefore inhibition of Jagged 1 (Alagille syndrome) (JAG1, Accession NM\_000214). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JAG1. DKFZP434P1750 (Accession NM\_015527) is another VGAM441 host target gene. DKFZP434P1750 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434P1750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434P1750 BINDING SITE, designated SEQ ID:17793, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20816] Another function of VGAM441 is therefore inhibition of DKFZP434P1750 (Accession NM\_015527). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434P1750. NCUBE1 (Accession NM\_016021) is another VGAM441 host target gene. NCUBE1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCUBE1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCUBE1 BINDING SITE, designated SEQ ID:18094, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20817] Another function of VGAM441 is therefore inhibition of NCUBE1 (Accession NM\_016021). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCUBE1.

NS1-BP (Accession XM\_051877) is another VGAM441 host target gene. NS1-BP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NS1-BP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NS1-BP BINDING SITE, designated SEQ ID:35914, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20818] Another function of VGAM441 is therefore inhibition of NS1-BP (Accession XM\_051877). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NS1-BP. LOC132720 (Accession XM\_059597) is another VGAM441 host target gene. LOC132720 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC132720, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC132720 BINDING SITE, designated SEQ ID:37028, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA,



also designated SEQ ID:3152.

[20819] Another function of VGAM441 is therefore inhibition of LOC132720 (Accession XM\_059597). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC132720. LOC146957 (Accession XM\_085652) is another VGAM441 host target gene. LOC146957 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146957, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146957 BINDING SITE, designated SEQ ID:38283, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20820] Another function of VGAM441 is therefore inhibition of LOC146957 (Accession XM\_085652). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146957. LOC158014 (Accession XM\_088442) is another VGAM441 host target gene. LOC158014 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158014, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158014 BINDING SITE, designated SEQ ID:39688, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20821] Another function of VGAM441 is therefore inhibition of LOC158014 (Accession XM\_088442). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158014. LOC51339 (Accession NM\_016651) is another VGAM441 host target gene. LOC51339 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51339, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51339 BINDING SITE, designated SEQ ID:18770, to the nucleotide sequence of VGAM441 RNA, herein designated VGAM RNA, also designated SEQ ID:3152.

[20822] Another function of VGAM441 is therefore inhibition of LOC51339 (Accession NM\_016651). Accordingly, utilities of VGAM441 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC51339. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 442 (VGAM442) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20823] VGAM442 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM442 was detected is described hereinabove with reference to Figs. 1–8.

[20824] VGAM442 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM442 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20825] VGAM442 gene encodes a VGAM442 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM442 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM442 precursor RNA is designated SEQ

ID:428, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:428 is located at position 78761 relative to the genome of Vaccinia Virus.

[20826] VGAM442 precursor RNA folds onto itself, forming VGAM442 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20827] An enzyme complex designated DICER COMPLEX, `dices` the VGAM442 folded precursor RNA into VGAM442 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM442 RNA is designated SEQ ID:3153, and is provided hereinbelow with reference to the sequence

listing part.

[20828] VGAM442 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM442 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM442 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20829] VGAM442 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM442 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM442 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM442 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM442 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20830] The complementary binding of VGAM442 RNA, herein designated VGAM RNA, to host target binding sites on VGAM442 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM442 host target RNA into VGAM442 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20831] It is appreciated that VGAM442 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM442 host target genes. The mRNA of each one of this plurality of VGAM442 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM442 RNA, herein designated VGAM

RNA, and which when bound by VGAM442 RNA causes inhibition of translation of respective one or more VGAM442 host target proteins.

[20832] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM442 gene, herein designated VGAM GENE, on one or more VGAM442 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20833] It is yet further appreciated that a function of VGAM442 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM442 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM442 correlate with, and may be deduced from, the identity of the host target genes which VGAM442 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20834] Nucleotide sequences of the VGAM442 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM442 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM442 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM442 are further described hereinbelow with reference to Table 1.

[20835] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM442 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM442 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20836] As mentioned hereinabove with reference to Fig. 1, a function of VGAM442 gene, herein designated VGAM is



inhibition of expression of VGAM442 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM442 correlate with, and may be deduced from, the identity of the target genes which VGAM442 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20837] Kallmann Syndrome 1 Sequence (KAL1, Accession NM\_000216) is a VGAM442 host target gene. KAL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KAL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KAL1 BINDING SITE, designated SEQ ID:5719, to the nucleotide sequence of VGAM442 RNA, herein designated VGAM RNA, also designated SEQ ID:3153.

[20838] A function of VGAM442 is therefore inhibition of Kallmann Syndrome 1 Sequence (KAL1, Accession NM\_000216). Accordingly, utilities of VGAM442 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KAL1. Synaptotagmin IV (SYT4, Accession XM\_031162) is another VGAM442 host target gene. SYT4 BINDING SITE is HOST TARGET binding site found in the

3` untranslated region of mRNA encoded by SYT4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYT4 BINDING SITE, designated SEQ ID:31292, to the nucleotide sequence of VGAM442 RNA, herein designated VGAM RNA, also designated SEQ ID:3153.

[20839] Another function of VGAM442 is therefore inhibition of Synaptotagmin IV (SYT4, Accession XM\_031162), a gene which may be involved in  $Ca^{2+}$ -dependent exocytosis of secretory vesicles or may serve as  $Ca^{2+}$  sensors in the process of vesicular trafficking and exocytosis. Accordingly, utilities of VGAM442 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYT4. The function of SYT4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200.KIAA0895 (Accession XM\_166573) is another VGAM442 host target gene. KIAA0895 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0895 BINDING SITE, designated SEQ ID:44544, to the nucleotide sequence of VGAM442 RNA, herein designated VGAM RNA, also designated SEQ ID:3153.

[20840] Another function of VGAM442 is therefore inhibition of KIAA0895 (Accession XM\_166573). Accordingly, utilities of VGAM442 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0895. LOC161589 (Accession XM\_090991) is another VGAM442 host target gene. LOC161589 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC161589, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161589 BINDING SITE, designated SEQ ID:40024, to the nucleotide sequence of VGAM442 RNA, herein designated VGAM RNA, also designated SEQ ID:3153.

[20841] Another function of VGAM442 is therefore inhibition of LOC161589 (Accession XM\_090991). Accordingly, utilities of VGAM442 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC161589. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 443 (VGAM443) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20842] VGAM443 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM443 was detected is described hereinabove with reference to Figs. 1–8.

[20843] VGAM443 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM443 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20844] VGAM443 gene encodes a VGAM443 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM443 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM443 precursor RNA is designated SEQ ID:429, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:429 is located at position 81960 relative to the genome of Vaccinia Virus.

[20845] VGAM443 precursor RNA folds onto itself, forming VGAM443 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20846] An enzyme complex designated DICER COMPLEX, `dices` the VGAM443 folded precursor RNA into VGAM443 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM443 RNA is designated SEQ ID:3154, and is provided hereinbelow with reference to the sequence listing part.

[20847] VGAM443 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM443 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM443 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20848] VGAM443 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM443 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM443 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM443 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM443 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[20849] The complementary binding of VGAM443 RNA, herein designated VGAM RNA, to host target binding sites on VGAM443 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM443 host target RNA into VGAM443 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20850] It is appreciated that VGAM443 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM443 host target genes. The mRNA of each one of this plurality of VGAM443 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM443 RNA, herein designated VGAM RNA, and which when bound by VGAM443 RNA causes in-

hibition of translation of respective one or more VGAM443 host target proteins.

[20851] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM443 gene, herein designated VGAM GENE, on one or more VGAM443 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20852] It is yet further appreciated that a function of VGAM443 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM443 include diagnosis, prevention and



treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM443 correlate with, and may be deduced from, the identity of the host target genes which VGAM443 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [20853] Nucleotide sequences of the VGAM443 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM443 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM443 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM443 are further described hereinbelow with reference to Table 1.
- [20854] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM443 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM443 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [20855] As mentioned hereinabove with reference to Fig. 1, a function of VGAM443 gene, herein designated VGAM is inhibition of expression of VGAM443 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM443 correlate with, and may be deduced from, the identity of the target genes which VGAM443 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20856] 2',3'-cyclic Nucleotide 3' Phosphodiesterase (CNP, Accession NM\_033133) is a VGAM443 host target gene. CNP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNP BINDING SITE, designated SEQ ID:26976, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20857] A function of VGAM443 is therefore inhibition of 2',3'-cyclic Nucleotide 3' Phosphodiesterase (CNP, Accession NM\_033133), a gene which can link tubulin to membranes and may regulate cytoplasmic microtubule distribution. Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNP. The function of CNP has been established by previous studies. Cyclic nucleotide phos-

phodiesterase is a useful marker of myelin. CNPase is a membrane-bound enzyme found at high concentrations in central nervous system myelin and in the outer segments of photoreceptors in the retina (Vogel and Thompson, 1988). Two proteins with CNP activity are known to exist in brain and lymphoid tissues. They appear to be the products of distinct but related mRNA species. Kurihara et al. (1990) showed that the 2 gene products can arise by translation of 2 mRNAs alternatively spliced from a single transcript. In bovine and human brain, there appears to be a single species of mRNA (Vogel and Thompson, 1988), and the bovine brain and retinal forms of the enzyme appear to be identical in sequence Bifulco et al. (2002) demonstrated that CNP is firmly associated with tubulin (OMIM Ref. No. 602529) from brain tissue and thyroid cells. They showed that CNP acts as a microtubule-associated protein in promoting microtubule assembly. This activity was found to reside in the C terminus of the enzyme. The authors concluded that CNP is a membrane-bound microtubule-associated protein that can link tubulin to membranes and may regulate cytoplasmic microtubule distribution

[20858] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

[20859] Vogel, U. S.; Thompson, R. J. : Molecular structure, localization, and possible functions of the myelin-associated enzyme 2-prime,3-prime-cyclic nucleotide 3-prime-phosphodiesterase. J. Neurochem. 50: 1667-1677, 1988. ; and

[20860] Bifulco, M.; Laezza, C.; Stingo, S.; Wolff, J. : 2-prime,3-prime-cyclic nucleotide 3-prime-phosphodiesterase: a membrane-bound, microtubule-associated protein and membrane anchor for tub.

[20861] Further studies establishing the function and utilities of CNP are found in John Hopkins OMIM database record ID 123830, and in cited publications numbered 4336-4337, 4334-4335, 4330-433 and 4338-4340 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437) is another VGAM443 host target gene. NCOA4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NCOA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of NCOA4 BINDING SITE, designated SEQ ID:11922, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20862] Another function of VGAM443 is therefore inhibition of Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437), a gene which Binds and activates androgen receptor (AR) in ligand-dependent manner. Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA4. The function of NCOA4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM420. Transcription Factor Binding to IGHM Enhancer 3 (TFE3, Accession NM\_006521) is another VGAM443 host target gene. TFE3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TFE3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TFE3 BINDING SITE, designated SEQ ID:13274, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA,

also designated SEQ ID:3154.

[20863] Another function of VGAM443 is therefore inhibition of Transcription Factor Binding to IGHM Enhancer 3 (TFE3, Accession NM\_006521), a gene which is a positive-acting transcription factor that binds to the immunoglobulin enhancer  $\mu$ E3 motif. Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TFE3. The function of TFE3 has been established by previous studies. TFE3, a member of the helix-loop-helix family of transcription factors, binds to the  $\mu$ -E3 motif of the immunoglobulin heavy-chain enhancer and is expressed in many cell types. Henthorn et al. (1991) localized the TFE3 gene to the proximal short arm of the X chromosome using a somatic cell hybrid panel. A frequent RsaI RFLP detected by the TFE3 cDNA was found and used to confirm this location by linkage analysis, which placed TFE3 near markers in Xp11.22. In the course of high-resolution comparative mapping of the proximal region of the mouse X chromosome, Blair et al. (1995) mapped the Tfe3 gene to the same region as the Gata1 gene (OMIM Ref. No. 305371). Heimann et al. (2001) identified the ASPSCR1 gene, which they called RCC17, partnered with TFE3 in two 5-year-old

Belgian girls of African origin in whom papillary renal cell carcinomas carried the translocation t(X;17)(p11.2;q25). In both patients, the t(X;17) fused the N terminal region of RCC17 to the C terminal region of TFE3 including the bHLH DNA-binding domain and the leucine zipper dimerization domain. The reciprocal fusion transcript TFE3/RCC17 was also expressed.

[20864] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20865] Heimann, P.; El Housni, H.; Ogur, G.; Weterman, M. A. J.; Petty, E. M.; Vassart, G. : Fusion of a novel gene, RCC17, to the TFE3 gene in t(X;17)(p11.2;q25.3)-bearing papillary renal cell carcinomas. Cancer Res. 61: 4130-4135, 2001. ; and

[20866] Blair, H. J.; Ho, M.; Monaco, A. P.; Fisher, S.; Craig, I. W.; Boyd, Y. : High-resolution comparative mapping of the proximal region of the mouse X chromosome. Genomics 28: 305-310, 199.

[20867] Further studies establishing the function and utilities of TFE3 are found in John Hopkins OMIM database record ID 314310, and in cited publications numbered 6569, 8207-8212, 1553, 8213-821 and 10617 listed in the bib-

liography section hereinbelow, which are also hereby incorporated by reference. Vacuolar Protein Sorting 26 (yeast) (VPS26, Accession NM\_004896) is another VGAM443 host target gene. VPS26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VPS26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VPS26 BINDING SITE, designated SEQ ID:11329, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20868] Another function of VGAM443 is therefore inhibition of Vacuolar Protein Sorting 26 (yeast) (VPS26, Accession NM\_004896), a gene which is a sorting protein—ensures the proper delivery of organelle-specific proteins. Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VPS26. The function of VPS26 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM315. Caspase Recruitment Domain Family, Member 6 (CARD6, Accession



NM\_032587) is another VGAM443 host target gene. CARD6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CARD6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CARD6 BINDING SITE, designated SEQ ID:26322, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20869] Another function of VGAM443 is therefore inhibition of Caspase Recruitment Domain Family, Member 6 (CARD6, Accession NM\_032587). Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CARD6. DKFZp761K1423 (Accession NM\_018422) is another VGAM443 host target gene. DKFZp761K1423 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZp761K1423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761K1423 BINDING SITE, designated

SEQ ID:20475, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20870] Another function of VGAM443 is therefore inhibition of DKFZp761K1423 (Accession NM\_018422). Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761K1423. KIAA0090 (Accession XM\_114045) is another VGAM443 host target gene. KIAA0090 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0090, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0090 BINDING SITE, designated SEQ ID:42655, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20871] Another function of VGAM443 is therefore inhibition of KIAA0090 (Accession XM\_114045). Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0090. KIAA0543 (Accession XM\_044213) is another VGAM443 host target gene. KIAA0543 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0543, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0543 BINDING SITE, designated SEQ ID:34180, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20872] Another function of VGAM443 is therefore inhibition of KIAA0543 (Accession XM\_044213). Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0543. Lymphocyte Antigen 75 (LY75, Accession NM\_002349) is another VGAM443 host target gene. LY75 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LY75, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LY75 BINDING SITE, designated SEQ ID:8152, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20873] Another function of VGAM443 is therefore inhibition of

Lymphocyte Antigen 75 (LY75, Accession NM\_002349). Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LY75. LOC146179 (Accession XM\_085354) is another VGAM443 host target gene. LOC146179 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146179, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146179 BINDING SITE, designated SEQ ID:38077, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20874] Another function of VGAM443 is therefore inhibition of LOC146179 (Accession XM\_085354). Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146179. LOC221399 (Accession XM\_168134) is another VGAM443 host target gene. LOC221399 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221399, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC221399 BINDING SITE, designated SEQ ID:45053, to the nucleotide sequence of VGAM443 RNA, herein designated VGAM RNA, also designated SEQ ID:3154.

[20875] Another function of VGAM443 is therefore inhibition of LOC221399 (Accession XM\_168134). Accordingly, utilities of VGAM443 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221399. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 444 (VGAM444) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20876] VGAM444 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM444 was detected is described hereinabove with reference to Figs. 1–8.

[20877] VGAM444 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM444 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[20878] VGAM444 gene encodes a VGAM444 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM444 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM444 precursor RNA is designated SEQ ID:430, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:430 is located at position 81204 relative to the genome of Vaccinia Virus.

[20879] VGAM444 precursor RNA folds onto itself, forming VGAM444 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20880] An enzyme complex designated DICER COMPLEX, `dices` the VGAM444 folded precursor RNA into VGAM444 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 51%) nucleotide sequence of VGAM444 RNA is designated SEQ ID:3155, and is provided hereinbelow with reference to the sequence listing part.

[20881] VGAM444 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM444 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM444 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20882] VGAM444 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM444 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM444 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM444 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM444 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20883] The complementary binding of VGAM444 RNA, herein designated VGAM RNA, to host target binding sites on VGAM444 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM444 host target RNA into VGAM444 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.



[20884] It is appreciated that VGAM444 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM444 host target genes. The mRNA of each one of this plurality of VGAM444 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM444 RNA, herein designated VGAM RNA, and which when bound by VGAM444 RNA causes inhibition of translation of respective one or more VGAM444 host target proteins.

[20885] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM444 gene, herein designated VGAM GENE, on one or more VGAM444 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20886] It is yet further appreciated that a function of VGAM444 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM444 correlate with, and may be deduced from, the identity of the host target genes which VGAM444 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20887] Nucleotide sequences of the VGAM444 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM444 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM444 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM444 are further described hereinbelow with reference to Table 1.

[20888] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM444 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM444 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20889] As mentioned hereinabove with reference to Fig. 1, a function of VGAM444 gene, herein designated VGAM is inhibition of expression of VGAM444 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM444 correlate with, and may be deduced from, the identity of the target genes which VGAM444 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20890] Discs, Large (Drosophila) Homolog 5 (DLG5, Accession XM\_096398) is a VGAM444 host target gene. DLG5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DLG5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLG5 BINDING SITE, designated SEQ ID:40336, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20891] A function of VGAM444 is therefore inhibition of Discs, Large (Drosophila) Homolog 5 (DLG5, Accession XM\_096398), a gene which may transmit extracellular signals to inhibit cell proliferation. Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLG5. The function of DLG5 has been established by previous studies. Vertebrate homologs of the Drosophila discs large (dlg) gene are members of the MAGUK (membrane-associated guanylate kinase) family. See 602887. MAGUK proteins contain PDZ motifs, an SH3 domain, and a guanylate kinase (GUK)-homologous region. Both the PDZ and GUK domains are thought to contribute to protein-protein interactions. By searching an EST database for sequences related to Drosophila dlg, Nakamura et al. (1998) identified cDNAs encoding a novel human homolog. Northern blot analysis revealed that the 9.4-kb transcript was highly expressed in placenta and prostate, as well as in several other tissues, leading the authors to designate the gene PDLG (placenta and prostate DLG). An additional 8.8-kb PDLG mRNA was detected in thyroid. The predicted 859-amino acid PDLG protein contains 3 PDZ domains, an SH3 domain, and a

GUK region. PDLG is 45% and 40% identical to DLG1 (OMIM Ref. No. 601014) and *Drosophila* dlg, respectively. Western blot analysis of extracts of human prostate tissue and various cell lines showed that PDLG has an apparent molecular mass of 105 kD. Immunofluorescence experiments indicated that PDLG is localized at the plasma membrane and cytoplasm, and is expressed in the gland epithelial cells of normal prostate tissue but not in prostate cell lines. Using a yeast 2-hybrid screen, Nakamura et al. (1998) determined that PDLG interacts with the GUK domain of p55 (MPP1; 305360), a palmitoylated erythrocyte membrane MAGUK protein. The authors suggested that PDLG and p55 form a heteromeric MAGUK complex at the plasma membrane and cluster various intracellular molecules to play roles in maintaining the structure of epithelial cells and transmitting extracellular signals to the membrane and cytoskeleton. Independently, Nagase et al. (1998) identified KIAA0583, a DLG5 cDNA. By radiation hybrid analysis, they mapped the DLG5 gene to chromosome 10. Using the same technique, Nakamura et al. (1998) refined the localization of the DLG5 gene to 10q23.

[20892] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

[20893] Nagase, T.; Ishikawa, K.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro. DNA Res. 5: 31–39, 1998.  
; and

[20894] Nakamura, H.; Sudo, T.; Tsuiki, H.; Miyake, H.; Morisaki, T.; Sasaki, J.; Masuko, N.; Kochi, M.; Ushio, Y.; Saya, H. : Identification of a novel human homolog of the Drosophila dlg, P-d.

[20895] Further studies establishing the function and utilities of DLG5 are found in John Hopkins OMIM database record ID 604090, and in cited publications numbered 6735 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fc Fragment of IgG, Low Affinity IIa, Receptor For (CD32) (FCGR2A, Accession XM\_086483) is another VGAM444 host target gene. FCGR2A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FCGR2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of FCGR2A BINDING SITE, designated SEQ ID:38699, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20896] Another function of VGAM444 is therefore inhibition of Fc Fragment of IgG, Low Affinity Ila, Receptor For (CD32) (FCGR2A, Accession XM\_086483), a gene which binds IgG immune complexes; member of the immunoglobulin superfamily. Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FCGR2A. The function of FCGR2A has been established by previous studies. Receptors for the Fc portion of IgG play an essential role in the protection of the organism against foreign antigens by removing antigen-antibody complexes from the circulation. Receptors are present on monocytes, macrophages, neutrophils, natural killer (NK) cells, and T and B lymphocytes, and they participate in diverse functions such as phagocytosis of immune complexes and modulation of antibody production by B cells. Hibbs et al. (1988) isolated cDNA clones for the FcGR gene by cross-species hybridization by probing cDNA libraries with a low-affinity FcGR beta-1

cDNA clone from mouse, as well as a pool of oligonucleotides constructed from the nucleotide sequence of this FcGR. Analysis of the amino acid sequence predicted from cDNA clones indicated that the human FcGR protein is synthesized with a 34-amino acid leader and that the mature protein is composed of 281 amino acids. The extracellular region of this FcGR was divided into 2 domains, which were very similar to each other and to the corresponding regions of both mouse alpha and beta FcGRs and showed a clear relationship to immunoglobulin variable regions. Grundy et al. (1988) mapped the immunoglobulin Fc receptor II and Fc receptor III genes to chromosome 1 by means of spot-blot analysis of sorted chromosomes. By hybridizing each probe to human DNA digested with 8 different 'rare-cutting' restriction enzymes and separated by pulsed field gel electrophoresis, Grundy et al. (1988) showed that the 2 genes mapped to the same fragment, the smallest of which was 250 kb long. Peltz et al. (1989) showed physical linkage of the 2 genes within a maximum distance of 200 kb. The conclusion on the basis of Southern and in situ data of Grundy et al. (1989) that there are three 8- to 10-kb Fc-gamma-RII loci per haploid genome was confirmed by Qiu et al. (1990), who



named the genes A, A-prime, and B to reflect their homology and presumed evolution. Lebo et al. (1991) noted that occasionally these 3 genes, which lie within a 200-kb region, could be resolved in individual metaphase chromatids by multicolor fluorescence in situ hybridization. By in situ hybridization, Sammartino et al. (1988) assigned the IGFR2 gene to 1q23-q24. In the course of constructing a physical map of human 1q21-q23, Oakey et al. (1992) placed FCGR2A in that region, close to MPP (OMIM Ref. No. 159440) and APOA2 (OMIM Ref. No. 107670). The homologous gene in the mouse, Ly-17, maps to mouse chromosome 1 (Hibbs et al., 1985). See review by Unkeless (1989).

[20897] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20898] Peltz, G. A.; Grundy, H. O.; Lebo, R. V.; Yssel, H.; Barsh, G. S.; Moore, K. W. : Human Fc-gamma-RIII: cloning, expression, and identification of the chromosomal locus of two Fc receptors for IgG. Proc. Nat. Acad. Sci. 86: 1013-1017, 1989. ; and

[20899] Salmon, J. E.; Millard, S.; Schachter, L. A.; Arnett, F. C.; Ginzler, E. M.; Gourley, M. F.; Ramsey-Goldman, R.; Peter-

son, M. G. E.; Kimberly, R. P. : Fc-gamma-RIIA alleles are heritabl.

[20900] Further studies establishing the function and utilities of FCGR2A are found in John Hopkins OMIM database record ID 146790, and in cited publications numbered 392 and 3930–3940 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Lysophospholipase I (LYPLA1, Accession NM\_006330) is another VGAM444 host target gene. LYPLA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LYPLA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LYPLA1 BINDING SITE, designated SEQ ID:13027, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20901] Another function of VGAM444 is therefore inhibition of Lysophospholipase I (LYPLA1, Accession NM\_006330). Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LYPLA1. Prodynorphin (PDYN, Accession

NM\_024411) is another VGAM444 host target gene. PDYN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDYN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDYN BINDING SITE, designated SEQ ID:23652, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20902] Another function of VGAM444 is therefore inhibition of Prodynorphin (PDYN, Accession NM\_024411), a gene which is an opioid peptide acting on the kappa-receptor . Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDYN. The function of PDYN has been established by previous studies. Horikawa et al. (1983) cloned a human genomic DNA segment containing the preproenkephalin B gene. From studies of the gene for porcine preproenkephalin B, it is known to contain the determinants for neoendorphin, dynorphin, and leumorphin (containing rimorphin in its amino-terminus). These opioid peptides, each with a leucine-enkephalin structure, act on the kappa-receptor. The structural organization of

the gene resembles that of the genes encoding the other opioid peptide precursors, preproenkephalin A (OMIM Ref. No. 131330) and preproopiomelanocortin (OMIM Ref. No. 176830). Litt et al. (1987, 1988) assigned the PDYN gene to human chromosome 20 by Southern blot analysis of DNAs from a rodent–human somatic cell hybrid panel. In situ hybridization to metaphase chromosomes confirmed this assignment and indicated the regional localization to be 20pter–p12. Summar et al. (1990) demonstrated very close linkage of PDYN with ARVP (OMIM Ref. No. 192340) and OT (OMIM Ref. No. 167050); no recombinants were found with a lod score of 5.2. This cluster of genes appears to be located about 15 cM distal to D20S5, which is located near the middle of the short arm at 20p12.21. In connection with this close proximity of the genes, it is noteworthy that the ARVP and PDYN peptides are coexcreted in the same neurosecretory granules of some pituitary axons and that increased transcription of both genes occurs with osmotic stimulation. Temporal lobe epilepsy is a common, heterogeneous epilepsy syndrome with both environmental and genetic factors playing a role in its etiology (Berkovic et al., 1996; Cendes et al., 1998). Ottman et al. (1995) localized a gene for partial epilepsy with au–

ditary features (OMIM Ref. No. 600512) to 10q; by a positional candidate gene approach, Kalachikov et al. (2002) found that mutations in the LGI1 gene are responsible for this form of temporal lobe epilepsy. Stogmann et al. (2002) performed a case control association study in 155 patients with nonlesional temporal lobe epilepsy and 202 controls, and found that the PDYN promoter low-expression L alleles (1 or 2 repeats) conferred an increased risk for temporal lobe epilepsy in patients with a family history for seizures. Irrespective of the familial background, L homozygotes displayed a higher risk for secondarily generalized seizures and status epilepticus.

[20903] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20904] Summar, M. L.; Phillips, J. A., III; Battey, J.; Castiglione, C. M.; Kidd, K. K.; Maness, K. J.; Weiffenbach, B.; Gravius, T. C. : Linkage relationships of human arginine vasopressin-neurophysin-II and oxytocin-neurophysin-I to prodynorphin and other loci on chromosome 20. Molec. Endocr. 4: 947-950, 1990. ; and

[20905] Stogmann, E.; Zimprich, A.; Baumgartner, C.; Aull-Watschinger, S.; Holtt, V.; Zimprich, F. : A functional poly-

morphism in the prodynorphin gene promoter is associated with temporal lobe.

[20906] Further studies establishing the function and utilities of PDYN are found in John Hopkins OMIM database record ID 131340, and in cited publications numbered 3568–3570, 4227–356 and 4571–4574 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. V-ski Sarcoma Viral Oncogene Homolog (avian) (SKI, Accession NM\_003036) is another VGAM444 host target gene. SKI BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SKI, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SKI BINDING SITE, designated SEQ ID:8988, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20907] Another function of VGAM444 is therefore inhibition of V-ski Sarcoma Viral Oncogene Homolog (avian) (SKI, Accession NM\_003036). Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SKI. KIAA0652 (Accession NM\_014741) is another VGAM444 host target

gene. KIAA0652 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0652, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0652 BINDING SITE, designated SEQ ID:16408, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20908] Another function of VGAM444 is therefore inhibition of KIAA0652 (Accession NM\_014741). Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0652. MGC2452 (Accession NM\_032644) is another VGAM444 host target gene. MGC2452 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC2452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2452 BINDING SITE, designated SEQ ID:26369, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20909] Another function of VGAM444 is therefore inhibition of MGC2452 (Accession NM\_032644). Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2452. Phospholipase A2, Group VI (cytosolic, calcium-independent) (PLA2G6, Accession XM\_039248) is another VGAM444 host target gene. PLA2G6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLA2G6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLA2G6 BINDING SITE, designated SEQ ID:33029, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20910] Another function of VGAM444 is therefore inhibition of Phospholipase A2, Group VI (cytosolic, calcium-independent) (PLA2G6, Accession XM\_039248). Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLA2G6. LOC145447 (Accession XM\_085133) is another VGAM444 host target gene. LOC145447 BINDING SITE is HOST TARGET binding site found in the 5' un-



translated region of mRNA encoded by LOC145447, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145447 BINDING SITE, designated SEQ ID:37861, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20911] Another function of VGAM444 is therefore inhibition of LOC145447 (Accession XM\_085133). Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145447. LOC149711 (Accession XM\_097720) is another VGAM444 host target gene. LOC149711 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149711, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149711 BINDING SITE, designated SEQ ID:41071, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20912] Another function of VGAM444 is therefore inhibition of LOC149711 (Accession XM\_097720). Accordingly, utilities

of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149711. LOC253786 (Accession XM\_173109) is another VGAM444 host target gene. LOC253786 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253786, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253786 BINDING SITE, designated SEQ ID:46363, to the nucleotide sequence of VGAM444 RNA, herein designated VGAM RNA, also designated SEQ ID:3155.

[20913] Another function of VGAM444 is therefore inhibition of LOC253786 (Accession XM\_173109). Accordingly, utilities of VGAM444 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253786. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 445 (VGAM445) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20914] VGAM445 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM445 was detected is described hereinabove with reference to Figs. 1–8.

[20915] VGAM445 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Papillomavirus Type 17. VGAM445 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20916] VGAM445 gene encodes a VGAM445 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM445 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM445 precursor RNA is designated SEQ ID:431, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:431 is located at position 358 relative to the genome of Human Papillomavirus Type 17.

[20917] VGAM445 precursor RNA folds onto itself, forming VGAM445 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20918] An enzyme complex designated DICER COMPLEX, `dices` the VGAM445 folded precursor RNA into VGAM445 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM445 RNA is designated SEQ ID:3156, and is provided hereinbelow with reference to the sequence listing part.

[20919] VGAM445 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM445 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM445 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[20920] VGAM445 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM445 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM445 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM445 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM445 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[20921] The complementary binding of VGAM445 RNA, herein designated VGAM RNA, to host target binding sites on VGAM445 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM445 host target RNA into VGAM445 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20922] It is appreciated that VGAM445 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM445 host target genes. The mRNA of each one of this plurality of VGAM445 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM445 RNA, herein designated VGAM RNA, and which when bound by VGAM445 RNA causes inhibition of translation of respective one or more VGAM445 host target proteins.

[20923] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM445 gene, herein designated VGAM GENE, on one or more VGAM445 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20924] It is yet further appreciated that a function of VGAM445 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of viral infection by Human Papillomavirus Type 17. Specific functions, and accordingly utilities, of VGAM445 correlate with, and may be deduced from, the identity of the host target genes which VGAM445 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20925] Nucleotide sequences of the VGAM445 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM445 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM445 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM445 are further  
described hereinbelow with reference to Table 1.

[20926] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM445 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM445 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[20927] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM445 gene, herein designated VGAM is  
inhibition of expression of VGAM445 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM445 correlate with, and may be deduced  
from, the identity of the target genes which VGAM445  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[20928] Annexin A4 (ANXA4, Accession XM\_031596) is a  
VGAM445 host target gene. ANXA4 BINDING SITE is HOST



TARGET binding site found in the 3' untranslated region of mRNA encoded by ANXA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANXA4 BINDING SITE, designated SEQ ID:31444, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20929] A function of VGAM445 is therefore inhibition of Annexin A4 (ANXA4, Accession XM\_031596), a gene which inhibits phospholipase\_A2 activity. Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANXA4. The function of ANXA4 has been established by previous studies. The annexins, or lipocortins, are a family of calcium-dependent phospholipid-binding proteins whose normal function is uncertain. Annexin IV, otherwise known as placental anticoagulant protein II, was 1 of the 4 annexins isolated from human placenta on the basis of their in vitro anticoagulant activity. Grundmann et al. (1988) reported a cDNA clone for annexin IV. Hauptmann et al. (1989) showed that annexin IV has 45 to 59% identity with other members of the annexin family. By PCR analysis of

somatic cell hybrids and in situ hybridization with a cDNA probe, Tait et al. (1992) mapped the human ANXA4 gene to 2p13. Genomic Southern blotting with a cDNA probe indicated a gene size of 18– to 56–kb. DNA sequence analysis demonstrated a single intron with exon–intron boundaries in exactly the same position as in the mouse annexin I and annexin II genes. Barrow et al. (1994) demonstrated that the Anxa4 gene is located on mouse chromosome 6 in a region of conserved synteny with human chromosome 2

[20930] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20931] Barrow, L. L.; Simin, K.; Jones, J. M.; Lee, D. C.; Meisler, M. H. : Conserved linkage of early growth response 4, annexin 4, and transforming growth factor alpha on mouse chromosome 6. *Genomics* 19: 388–390, 1994. ; and

[20932] Grundmann, U.; Amann, E.; Abel, K.–J.; Kupper, H. A. : Isolation and expression of cDNA coding for a new member of the phospholipase A2 inhibitor family. *Behring Inst. Mitt.* 82: 59–67.

[20933] Further studies establishing the function and utilities of ANXA4 are found in John Hopkins OMIM database record

ID 106491, and in cited publications numbered 11668–4844 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Adenomatosis Polyposis Coli (APC, Accession NM\_000038) is another VGAM445 host target gene. APC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APC BINDING SITE, designated SEQ ID:5480, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20934] Another function of VGAM445 is therefore inhibition of Adenomatosis Polyposis Coli (APC, Accession NM\_000038). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APC. Centaurin, Delta 1 (CENTD1, Accession NM\_139182) is another VGAM445 host target gene. CENTD1 BINDING SITE1 and CENTD1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CENTD1, corresponding to HOST TARGET binding sites such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CENTD1 BINDING SITE1 and CENTD1 BINDING SITE2, designated SEQ ID:29197 and SEQ ID:17560 respectively, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20935] Another function of VGAM445 is therefore inhibition of Centaurin, Delta 1 (CENTD1, Accession NM\_139182), a gene which is involved in cell signaling/communication. Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CENTD1. The function of CENTD1 has been established by previous studies. By screening brain cDNAs for the potential to encode proteins that are at least 50 kD, Nagase et al. (1998) identified a partial cDNA encoding CENTD1, which they called KIAA0580. The protein was predicted to be involved in cell signaling/communication. RT-PCR analysis detected expression of KIAA0580 in all tissues tested except skeletal muscle. By searching sequence databases, followed by 5-prime RACE, Miura et al. (2002) obtained full-length cDNAs encoding CENTD1 and CENTD2 (OMIM Ref. No. 606646), which they called ARAP2 and ARAP1, respectively. Like ARAP1, the

1,704-amino acid ARAP2 protein contains ARF-GAP (see OMIM Ref. No. 103180), RHO-GAP (see OMIM Ref. No. 602732), ankyrin repeat (see OMIM Ref. No. 605787), RAS (OMIM Ref. No. 190020)-associating, and 5 pleckstrin (OMIM Ref. No. 173570) homology (PH) domains. However, unlike ARAP1, ARAP2 also has a sterile alpha motif (SAM) domain like that found in EphA receptor (see OMIM Ref. No. 179610) and a region of homology to the switch-2 domain of RAB13 (OMIM Ref. No. 602672). The RHO-GAP domain of ARAP2 lacks the predicted catalytic arginine and is therefore unlikely to have RHO-GAP activity. Northern blot analysis showed that ARAP2 is much more variably expressed than ARAP1. The highest ARAP2 expression levels were in brain, thymus, spleen, kidney, peripheral blood leukocytes, lymph node, spinal cord, and thyroid. Two messages at 7.5 and 11 kb were found in brain, and 7.5- and 8.5-kb messages were found in thymus, spleen, kidney, peripheral blood leukocytes, and lymph node. Of the hematopoietic tissues examined, only bone marrow did not show ARAP2 expression.

[20936] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [20937] Miura, K.; Jacques, K. M.; Stauffer, S.; Kubosaki, A.; Zhu, K.; Hirsch, D. S.; Resau, J.; Zheng, Y.; Randazzo, P. A. : ARAP1: a point of convergence for Arf and Rho signaling. Molec. Cell 9: 109–119, 2002. ; and
- [20938] Nagase, T.; Ishikawa, K.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 10.
- [20939] Further studies establishing the function and utilities of CENTD1 are found in John Hopkins OMIM database record ID 606645, and in cited publications numbered 612 and 6735 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Guanine Nucleotide Binding Protein (G protein), Beta Polypeptide 1 (GNB1, Accession NM\_002074) is another VGAM445 host target gene. GNB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GNB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GNB1 BINDING SITE, designated SEQ ID:7847, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ

ID:3156.

[20940] Another function of VGAM445 is therefore inhibition of Guanine Nucleotide Binding Protein (G protein), Beta Polypeptide 1 (GNB1, Accession NM\_002074). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNB1. Janus Kinase 2 (a protein tyrosine kinase) (JAK2, Accession NM\_004972) is another VGAM445 host target gene. JAK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JAK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JAK2 BINDING SITE, designated SEQ ID:11416, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20941] Another function of VGAM445 is therefore inhibition of Janus Kinase 2 (a protein tyrosine kinase) (JAK2, Accession NM\_004972), a gene which tyrosine kinase of the non-receptor type, involved in interleukin 3 signal transduction. Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical condi-

tions associated with JAK2. The function of JAK2 has been established by previous studies. JAK2 kinase is a member of a family of tyrosine kinases involved in cytokine receptor signaling. See 147795 for background information on Janus kinases. In addition to its role as a kidney cytokine regulating hematopoiesis, erythropoietin (OMIM Ref. No. 133170) is also produced in the brain after oxidative or nitrosative stress. The transcription factor HIF1 (OMIM Ref. No. 603348) upregulates erythropoietin following hypoxic stimuli. Digicaylioglu and Lipton (2001) demonstrated that preconditioning with erythropoietin protects neurons in models of ischemic and degenerative damage due to excitotoxins and consequent generation of free radicals, including nitric oxide. Activation of neuronal erythropoietin receptors (EPOR; 133171) prevents apoptosis induced by NMDA or nitric oxide by triggering crosstalk between the signaling pathways JAK2 and NFkB (see OMIM Ref. No. 164011). Digicaylioglu and Lipton (2001) demonstrated that erythropoietin receptor-mediated activation of JAK2 leads to phosphorylation of the inhibitor of NFkB (I-kappa-B-alpha; 164008), subsequent nuclear translocation of the transcription factor NFkB, and NFkB-dependent transcription of neuroprotective genes. Trans-



fection of cerebrocortical neurons with a dominant interfering form of JAK2 or an I-kappa-B-alpha superrepressor blocks erythropoietin-mediated prevention of neuronal apoptosis. Thus, neuronal erythropoietin receptors activate a neuroprotective pathway that is distinct from previously well characterized JAK and NFkB functions. Moreover, this erythropoietin effect may underlie neuroprotection mediated by hypoxic-ischemic preconditioning.

Huang et al. (2001) showed that JAK2, and more specifically just its intact N-terminal domain, binds to EPOR in the endoplasmic reticulum and promotes its cell surface expression. This interaction was specific, as JAK1 had no effect. Residues 32 to 58 of the JAK2 JH7 domain were required for EPOR surface expression. Alanine scanning mutagenesis of the EPOR membrane proximal region revealed 2 modes of EPOR-JAK2 interaction. A continuous block of EPOR residues was required for functional, ligand-independent binding to JAK2 and cell surface receptor expression, whereas 4 specific residues were essential in switching on prebound JAK2 after ligand binding. Thus, in addition to its kinase activity required for cytokine receptor signaling, JAK is also an essential subunit required for surface expression of cytokine receptors. Animal

model experiments lend further support to the function of JAK2. Neubauer et al. (1998) also performed a targeted inactivation of Jak2 in mice. Jak2  $-/-$  embryos were anemic and died around day 12.5 postcoitum. Primitive erythrocytes were found, but definitive erythropoiesis was absent. Compared to erythropoietin receptor-deficient mice, the phenotype of Jak2 deficiency was more severe. Fetal liver BFU-E and CFU-E colonies were completely absent. However, multilineage hematopoietic stem cells (CD34-low, c-kit-pos) were found, and B lymphopoiesis appeared intact. In contrast to IFN-alpha stimulation, Jak2  $-/-$  cells did not respond to IFN-gamma. Jak2  $-/-$  embryonic stem cells were competent for LIF signaling. These data also demonstrated that Jak2 has pivotal functions for signal transduction of a set of cytokine receptors required in definitive erythropoiesis

[20942] It is appreciated that the abovementioned animal model for JAK2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[20943] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [20944] Neubauer, H.; Cumano, A.; Muller, M.; Wu, H.; Huffstadt, U.; Pfeffer, K. : Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* 93: 397–409, 1998. ; and
- [20945] Digicaylioglu, M.; Lipton, S. A. : Erythropoietin-mediated neuroprotection involves cross-talk between Jak2 and NF-kappa-B signalling cascades. *Nature* 412: 641–647, 2001.
- [20946] Further studies establishing the function and utilities of JAK2 are found in John Hopkins OMIM database record ID 147796, and in cited publications numbered 11678, 11675, 11679–11681, 1167 and 11682–11684 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Junctional Adhesion Molecule 3 (JAM3, Accession NM\_032801) is another VGAM445 host target gene. JAM3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JAM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JAM3 BINDING SITE, designated SEQ ID:26552, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20947] Another function of VGAM445 is therefore inhibition of Junctional Adhesion Molecule 3 (JAM3, Accession NM\_032801), a gene which is a member of the junctional adhesion molecule protein family. Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JAM3. The function of JAM3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200. Pyrimidinergic Receptor P2Y, G-protein Coupled, 6 (P2RY6, Accession NM\_004154) is another VGAM445 host target gene. P2RY6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P2RY6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P2RY6 BINDING SITE, designated SEQ ID:10352, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20948] Another function of VGAM445 is therefore inhibition of Pyrimidinergic Receptor P2Y, G-protein Coupled, 6 (P2RY6, Accession NM\_004154), a gene which mediates

cellular responses to nucleotides. Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P2RY6. The function of P2RY6 has been established by previous studies. Chang et al. (1995) discovered the first receptor of the P2Y6 type in rat. The human ortholog was identified by Communi et al. (1996). Maier et al. (1997) identified 3 isoforms of P2Y6 cDNA. Two contained the same contiguous open reading frames, but differed in their 5-prime untranslated regions and may, therefore, originate by alternative splicing; the third represented a pseudogene. Analysis of P2Y receptor subtype expression in human bone and 2 osteoblastic cell lines by RT-PCR showed that all known human P2Y receptor subtypes were expressed: P2Y1 (P2RY1; 601167), P2Y2, P2Y4, P2Y6, and P2Y7 (OMIM Ref. No. 601531). In contrast, analysis of brain-derived cell lines suggested that a selective expression of P2Y receptor subtypes occurs in brain tissue. By somatic cell hybridization, Pidlaoan et al. (1997) mapped the P2RY6 gene to 11q13.3-q13.5. By fluorescence in situ hybridization and by sequence tagged site (STS) mapping using the National Center for Biotechnology Information (NCBI) database, Somers et al. (1997) mapped the P2RY6

gene to 11q13.5, between polymorphic markers D11S1314 and D11S916. Further NCBI database analysis of the P2Y purinoceptor genes revealed that P2RY2 (OMIM Ref. No. 600041) maps within less than 4 cM of P2RY6. This was the first chromosomal clustering of this gene family to be described. By phylogenetic analysis of the P2Y purinoceptor family, Somers et al. (1997) demonstrated the presence of 5 evolutionary branches and suggested the occurrence of an ancient gene duplication event.

[20949] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[20950] Communi, D.; Parmentier, M.; Boeynaems, J.-M. : Cloning, functional expression and tissue distribution of the human P2Y6 receptor. *Biochem. Biophys. Res. Commun.* 222: 303–308, 1996. ; and

[20951] Maier, R.; Glatz, A.; Mosbacher, J.; Bilbe, G. : Cloning of P2Y6 cDNAs and identification of a pseudogene: comparison of P2Y receptor subtype expression in bone and brain tissues. *Bioch.*

[20952] Further studies establishing the function and utilities of P2RY6 are found in John Hopkins OMIM database record ID 602451, and in cited publications numbered 6319–632

and 7718 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Kinase (cAMP-dependent, catalytic) Inhibitor Alpha (PKIA, Accession NM\_006823) is another VGAM445 host target gene. PKIA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PKIA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PKIA BINDING SITE, designated SEQ ID:13698, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20953] Another function of VGAM445 is therefore inhibition of Protein Kinase (cAMP-dependent, catalytic) Inhibitor Alpha (PKIA, Accession NM\_006823). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PKIA. Retinoblastoma Binding Protein 5 (RBBP5, Accession NM\_005057) is another VGAM445 host target gene. RBBP5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RBBP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of RBBP5 BINDING SITE, designated SEQ ID:11484, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20954] Another function of VGAM445 is therefore inhibition of Retinoblastoma Binding Protein 5 (RBBP5, Accession NM\_005057). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RBBP5. Amyotrophic Lateral Sclerosis 2 (juvenile) Chromosome Region, Candidate 3 (ALS2CR3, Accession NM\_015049) is another VGAM445 host target gene. ALS2CR3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALS2CR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALS2CR3 BINDING SITE, designated SEQ ID:17408, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20955] Another function of VGAM445 is therefore inhibition of Amyotrophic Lateral Sclerosis 2 (juvenile) Chromosome Region, Candidate 3 (ALS2CR3, Accession NM\_015049).



Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALS2CR3. DKFZp566D133 (Accession XM\_050005) is another VGAM445 host target gene. DKFZp566D133 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp566D133, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp566D133 BINDING SITE, designated SEQ ID:35543, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20956] Another function of VGAM445 is therefore inhibition of DKFZp566D133 (Accession XM\_050005). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp566D133. DKFZp761O0113 (Accession NM\_018409) is another VGAM445 host target gene. DKFZp761O0113 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp761O0113, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BIND-

ING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761O0113 BINDING SITE, designated SEQ ID:20445, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20957] Another function of VGAM445 is therefore inhibition of DKFZp761O0113 (Accession NM\_018409). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761O0113. FLJ10330 (Accession NM\_018061) is another VGAM445 host target gene. FLJ10330 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10330, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10330 BINDING SITE, designated SEQ ID:19830, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20958] Another function of VGAM445 is therefore inhibition of FLJ10330 (Accession NM\_018061). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10330.

FLJ10525 (Accession NM\_018126) is another VGAM445 host target gene. FLJ10525 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10525 BINDING SITE, designated SEQ ID:19913, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20959] Another function of VGAM445 is therefore inhibition of FLJ10525 (Accession NM\_018126). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10525. FLJ14457 (Accession NM\_032788) is another VGAM445 host target gene. FLJ14457 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14457, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14457 BINDING SITE, designated SEQ ID:26541, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3156.

[20960] Another function of VGAM445 is therefore inhibition of FLJ14457 (Accession NM\_032788). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14457. FLJ20273 (Accession NM\_019027) is another VGAM445 host target gene. FLJ20273 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20273 BINDING SITE, designated SEQ ID:21112, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20961] Another function of VGAM445 is therefore inhibition of FLJ20273 (Accession NM\_019027). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20273. FLJ20986 (Accession NM\_024524) is another VGAM445 host target gene. FLJ20986 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20986, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20986 BINDING SITE, designated SEQ ID:23726, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20962] Another function of VGAM445 is therefore inhibition of FLJ20986 (Accession NM\_024524). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20986. KIAA0408 (Accession NM\_014702) is another VGAM445 host target gene. KIAA0408 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0408, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0408 BINDING SITE, designated SEQ ID:16230, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20963] Another function of VGAM445 is therefore inhibition of KIAA0408 (Accession NM\_014702). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0408. KIAA0676 (Accession NM\_015043) is another VGAM445 host target gene. KIAA0676 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0676, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0676 BINDING SITE, designated SEQ ID:17392, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20964] Another function of VGAM445 is therefore inhibition of KIAA0676 (Accession NM\_015043). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0676. KIAA0844 (Accession NM\_014951) is another VGAM445 host target gene. KIAA0844 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0844, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0844 BINDING SITE, designated SEQ ID:17282, to the

nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20965] Another function of VGAM445 is therefore inhibition of KIAA0844 (Accession NM\_014951). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0844. KIAA1327 (Accession XM\_051146) is another VGAM445 host target gene. KIAA1327 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1327, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1327 BINDING SITE, designated SEQ ID:35761, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20966] Another function of VGAM445 is therefore inhibition of KIAA1327 (Accession XM\_051146). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1327. KIAA1500 (Accession XM\_034353) is another VGAM445 host target gene. KIAA1500 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1500 BINDING SITE, designated SEQ ID:32063, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20967] Another function of VGAM445 is therefore inhibition of KIAA1500 (Accession XM\_034353). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1500. KIAA1617 (Accession XM\_166140) is another VGAM445 host target gene. KIAA1617 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1617, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1617 BINDING SITE, designated SEQ ID:43940, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20968] Another function of VGAM445 is therefore inhibition of KIAA1617 (Accession XM\_166140). Accordingly, utilities



of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1617. KIAA1826 (Accession XM\_040784) is another VGAM445 host target gene. KIAA1826 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1826 BINDING SITE, designated SEQ ID:33374, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20969] Another function of VGAM445 is therefore inhibition of KIAA1826 (Accession XM\_040784). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1826. MGC4737 (Accession NM\_031466) is another VGAM445 host target gene. MGC4737 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC4737, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4737

BINDING SITE, designated SEQ ID:25503, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20970] Another function of VGAM445 is therefore inhibition of MGC4737 (Accession NM\_031466). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4737. NDRG Family Member 4 (NDRG4, Accession NM\_020465) is another VGAM445 host target gene. NDRG4 BINDING SITE1 and NDRG4 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by NDRG4, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDRG4 BINDING SITE1 and NDRG4 BINDING SITE2, designated SEQ ID:21695 and SEQ ID:23210 respectively, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20971] Another function of VGAM445 is therefore inhibition of NDRG Family Member 4 (NDRG4, Accession NM\_020465). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with NDRG4. SMOC1 (Accession NM\_022137) is another VGAM445 host target gene. SMOC1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SMOC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMOC1 BINDING SITE, designated SEQ ID:22698, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20972] Another function of VGAM445 is therefore inhibition of SMOC1 (Accession NM\_022137). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMOC1. Signal Sequence Receptor, Gamma (translocon-associated protein gamma) (SSR3, Accession NM\_007107) is another VGAM445 host target gene. SSR3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SSR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSR3 BINDING SITE, designated SEQ ID:13968, to the nucleotide sequence of

VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20973] Another function of VGAM445 is therefore inhibition of Signal Sequence Receptor, Gamma (translocon-associated protein gamma) (SSR3, Accession NM\_007107). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSR3. Ubiquitin Specific Protease 22 (USP22, Accession XM\_042698) is another VGAM445 host target gene. USP22 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by USP22, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USP22 BINDING SITE, designated SEQ ID:33749, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20974] Another function of VGAM445 is therefore inhibition of Ubiquitin Specific Protease 22 (USP22, Accession XM\_042698). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USP22. Yes-associated Pro-

tein 1, 65kDa (YAP1, Accession NM\_006106) is another VGAM445 host target gene. YAP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by YAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of YAP1 BINDING SITE, designated SEQ ID:12747, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20975] Another function of VGAM445 is therefore inhibition of Yes-associated Protein 1, 65kDa (YAP1, Accession NM\_006106). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with YAP1. LOC147358 (Accession XM\_011089) is another VGAM445 host target gene. LOC147358 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC147358, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147358 BINDING SITE, designated SEQ ID:30166, to the nucleotide sequence of

VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20976] Another function of VGAM445 is therefore inhibition of LOC147358 (Accession XM\_011089). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147358. LOC151647 (Accession XM\_087261) is another VGAM445 host target gene. LOC151647 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151647, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151647 BINDING SITE, designated SEQ ID:39153, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20977] Another function of VGAM445 is therefore inhibition of LOC151647 (Accession XM\_087261). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151647. LOC163255 (Accession XM\_092121) is another VGAM445 host target gene. LOC163255 BINDING SITE1 through LOC163255 BINDING SITE3 are HOST TAR-

GET binding sites found in untranslated regions of mRNA encoded by LOC163255, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163255 BINDING SITE1 through LOC163255 BINDING SITE3, designated SEQ ID:40105, SEQ ID:40106 and SEQ ID:40104 respectively, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20978] Another function of VGAM445 is therefore inhibition of LOC163255 (Accession XM\_092121). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163255. LOC201164 (Accession XM\_113904) is another VGAM445 host target gene. LOC201164 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201164, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201164 BINDING SITE, designated SEQ ID:42526, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20979] Another function of VGAM445 is therefore inhibition of LOC201164 (Accession XM\_113904). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201164. LOC201895 (Accession XM\_114396) is another VGAM445 host target gene. LOC201895 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201895 BINDING SITE, designated SEQ ID:42925, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20980] Another function of VGAM445 is therefore inhibition of LOC201895 (Accession XM\_114396). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201895. LOC203523 (Accession XM\_114713) is another VGAM445 host target gene. LOC203523 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203523, corresponding to a HOST TARGET binding site such as BIND-



ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203523 BINDING SITE, designated SEQ ID:43052, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20981] Another function of VGAM445 is therefore inhibition of LOC203523 (Accession XM\_114713). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203523. LOC219690 (Accession XM\_167572) is another VGAM445 host target gene. LOC219690 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219690, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219690 BINDING SITE, designated SEQ ID:44704, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20982] Another function of VGAM445 is therefore inhibition of LOC219690 (Accession XM\_167572). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC219690. LOC253959 (Accession XM\_170749) is another VGAM445 host target gene. LOC253959 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253959, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253959 BINDING SITE, designated SEQ ID:45509, to the nucleotide sequence of VGAM445 RNA, herein designated VGAM RNA, also designated SEQ ID:3156.

[20983] Another function of VGAM445 is therefore inhibition of LOC253959 (Accession XM\_170749). Accordingly, utilities of VGAM445 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253959. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 446 (VGAM446) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[20984] VGAM446 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM446 was detected is described hereinabove with reference to Figs. 1–8.

[20985] VGAM446 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Papillomavirus Type 17. VGAM446 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[20986] VGAM446 gene encodes a VGAM446 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM446 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM446 precursor RNA is designated SEQ ID:432, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:432 is located at position 437 relative to the genome of Human Papillomavirus Type 17.

[20987] VGAM446 precursor RNA folds onto itself, forming VGAM446 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[20988] An enzyme complex designated DICER COMPLEX, `dices` the VGAM446 folded precursor RNA into VGAM446 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM446 RNA is designated SEQ ID:3157, and is provided hereinbelow with reference to the sequence listing part.

[20989] VGAM446 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM446 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM446 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[20990] VGAM446 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM446 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM446 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM446 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM446 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[20991] The complementary binding of VGAM446 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM446 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM446 host target RNA into VGAM446 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[20992] It is appreciated that VGAM446 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM446 host target genes. The mRNA of each one of this plurality of VGAM446 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM446 RNA, herein designated VGAM RNA, and which when bound by VGAM446 RNA causes inhibition of translation of respective one or more VGAM446 host target proteins.

[20993] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM446 gene, herein designated VGAM GENE, on one or more VGAM446 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[20994] It is yet further appreciated that a function of VGAM446 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM446 include diagnosis, prevention and treatment of viral infection by Human Papillomavirus Type 17. Specific functions, and accordingly utilities, of VGAM446 correlate with, and may be deduced from, the identity of the host target genes which VGAM446 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[20995] Nucleotide sequences of the VGAM446 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM446 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM446 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM446 are further described hereinbelow with reference to Table 1.

[20996] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM446 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM446 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[20997] As mentioned hereinabove with reference to Fig. 1, a function of VGAM446 gene, herein designated VGAM is inhibition of expression of VGAM446 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM446 correlate with, and may be deduced from, the identity of the target genes which VGAM446 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[20998] Transmembrane Protein 2 (TMEM2, Accession NM\_013390) is a VGAM446 host target gene. TMEM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMEM2, cor-



responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMEM2 BINDING SITE, designated SEQ ID:15041, to the nucleotide sequence of VGAM446 RNA, herein designated VGAM RNA, also designated SEQ ID:3157.

[20999] A function of VGAM446 is therefore inhibition of Transmembrane Protein 2 (TMEM2, Accession NM\_013390). Accordingly, utilities of VGAM446 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMEM2. KIAA0660 (Accession NM\_012297) is another VGAM446 host target gene. KIAA0660 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0660, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0660 BINDING SITE, designated SEQ ID:14659, to the nucleotide sequence of VGAM446 RNA, herein designated VGAM RNA, also designated SEQ ID:3157.

[21000] Another function of VGAM446 is therefore inhibition of KIAA0660 (Accession NM\_012297). Accordingly, utilities of VGAM446 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0660. LOC219940 (Accession XM\_167791) is another VGAM446 host target gene. LOC219940 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC219940, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219940 BINDING SITE, designated SEQ ID:44832, to the nucleotide sequence of VGAM446 RNA, herein designated VGAM RNA, also designated SEQ ID:3157.

[21001] Another function of VGAM446 is therefore inhibition of LOC219940 (Accession XM\_167791). Accordingly, utilities of VGAM446 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219940. LOC90750 (Accession XM\_033868) is another VGAM446 host target gene. LOC90750 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC90750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90750 BINDING SITE, designated SEQ ID:31967, to the

nucleotide sequence of VGAM446 RNA, herein designated VGAM RNA, also designated SEQ ID:3157.

[21002] Another function of VGAM446 is therefore inhibition of LOC90750 (Accession XM\_033868). Accordingly, utilities of VGAM446 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90750. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 447 (VGAM447) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21003] VGAM447 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM447 was detected is described hereinabove with reference to Figs. 1–8.

[21004] VGAM447 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Papillomavirus Type 40. VGAM447 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21005] VGAM447 gene encodes a VGAM447 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM447 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM447 precursor RNA is designated SEQ ID:433, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:433 is located at position 1456 relative to the genome of Human Papillomavirus Type 40.

[21006] VGAM447 precursor RNA folds onto itself, forming VGAM447 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21007] An enzyme complex designated DICER COMPLEX, `dices` the VGAM447 folded precursor RNA into VGAM447 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM447 RNA is designated SEQ ID:3158, and is provided hereinbelow with reference to the sequence listing part.

[21008] VGAM447 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM447 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM447 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[21009] VGAM447 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM447 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM447 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM447 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM447 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21010] The complementary binding of VGAM447 RNA, herein designated VGAM RNA, to host target binding sites on VGAM447 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM447 host target RNA into VGAM447 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21011] It is appreciated that VGAM447 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM447 host target genes. The mRNA of each one of this plurality of VGAM447 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM447 RNA, herein designated VGAM RNA, and which when bound by VGAM447 RNA causes inhibition of translation of respective one or more VGAM447 host target proteins.

[21012] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM447 gene, herein designated VGAM GENE, on one or more VGAM447 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[21013] It is yet further appreciated that a function of VGAM447 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of viral infection by Human Papillomavirus Type 40. Specific functions, and accordingly utilities, of VGAM447 correlate with, and may be deduced from, the identity of the host target genes which VGAM447 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21014] Nucleotide sequences of the VGAM447 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM447 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM447 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM447 are further described hereinbelow with reference to Table 1.

[21015] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM447 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM447 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21016] As mentioned hereinabove with reference to Fig. 1, a function of VGAM447 gene, herein designated VGAM is inhibition of expression of VGAM447 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM447 correlate with, and may be deduced from, the identity of the target genes which VGAM447 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21017] ATPase, Na<sup>+</sup>/K<sup>+</sup> Transporting, Alpha 2 (+) Polypeptide (ATP1A2, Accession NM\_000702) is a VGAM447 host target gene. ATP1A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP1A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP1A2 BINDING SITE, designated SEQ ID:6363, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21018] A function of VGAM447 is therefore inhibition of ATPase,

Na<sup>+</sup>/K<sup>+</sup> Transporting, Alpha 2 (+) Polypeptide (ATP1A2, Accession NM\_000702). Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP1A2. DNA (cytosine-5-)-methyltransferase 3-like (DNMT3L, Accession NM\_013369) is another VGAM447 host target gene. DNMT3L BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DNMT3L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNMT3L BINDING SITE, designated SEQ ID:15015, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21019] Another function of VGAM447 is therefore inhibition of DNA (cytosine-5-)-methyltransferase 3-like (DNMT3L, Accession NM\_013369), a gene which plays a role in de novo methylation of CpG islands. Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNMT3L. The function of DNMT3L has been established by previous studies. By database analysis, PCR with specific primers

based on predicted and trapped exon sequences, and screening of testis, fetal liver, placenta, and thymus mRNA and cDNA libraries, Aapola et al. (2000) isolated a cDNA encoding DNMT3L. Sequence analysis predicted that the 387-amino acid protein contains a cysteine-rich region with a novel ADD (for ATRX (OMIM Ref. No. 300032), DNMT3, and DNMT3L) C2-C2 zinc finger motif near an imperfect PHD zinc finger with C4-C4. RT-PCR analysis detected highest expression of DNMT3L in testis, followed by ovary, thymus, and fetal thymus. Northern blot analysis failed to detect expression of DNMT3L. By genomic sequence analysis, Aapola et al. (2000) determined that the DNMT3L gene contains 12 exons and spans 16 kb. The translation initiation codon is in exon 2. The authors detected a splice variant lacking exon 8. Animal model experiments lend further support to the function of DNMT3L. By disrupting homologous recombination in mouse embryonic stem cells, Bourc'his et al. (2001) generated viable but sterile mice with mutated Dnmt3l (termed Dnmt3lG) in which male testes had severe hypogonadism and a Sertoli cell-only phenotype. The heterozygous offspring of females with Dnmt3lG failed to develop past 9.5 days postcoitum due to embryonic rather than

uterine defects. Bisulfite genomic sequence analysis of the differentially methylated region (DMR) of imprinted and maternally repressed genes such as *Snrpn* (OMIM Ref. No. 182279) detected undermethylation of oocytes from *Dnmt3l*G homozygous females, showing that *Dnmt3l* is required for the establishment of maternal methylation imprints. Heterozygous embryos from *Dnmt3l*G homozygotes displayed biallelic expression of genes that are normally expressed only from the allele of paternal origin. Bourc'h et al. (2001) concluded that DNMT3L is required specifically for the establishment of genomic imprints but is dispensable for their propagation, and it is essential for the de novo methylation of single-copy DNA sequences. The authors proposed that DNMT3L is likely to function as a regulator of methylation at imprinted loci rather than a DNA cytosine methyltransferase because of a lack of catalytic motifs in its sequence.

[21020] It is appreciated that the abovementioned animal model for DNMT3L is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21021] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [21022] Aapola, U.; Shibuya, K.; Scott, H. S.; Ollila, J.; Vihinen, M.; Heino, M.; Shintani, A.; Kawasaki, K.; Minoshima, S.; Krohn, K.; Antonarakis, S. E.; Shimizu, N.; Kudoh, J.; Peterson, P. : Isolation and initial characterization of a novel zinc finger gene, DNMT3L, on 21q22.3, related to the cysteine-5-methyltransferase 3 gene family. *Genomics* 65: 293-298, 2000. ; and
- [21023] Bourc'his, D.; Xu, G.-L.; Lin, C.-S.; Bollman, B.; Bestor, T. H. : Dnmt3L and the establishment of maternal genomic imprints. *Science* 294: 2536-2539, 2001.
- [21024] Further studies establishing the function and utilities of DNMT3L are found in John Hopkins OMIM database record ID 606588, and in cited publications numbered 6277-6278 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DXS1283E (Accession XM\_047871) is another VGAM447 host target gene. DXS1283E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DXS1283E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

DXS1283E BINDING SITE, designated SEQ ID:35062, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21025] Another function of VGAM447 is therefore inhibition of DXS1283E (Accession XM\_047871). Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DXS1283E. Neuronal Pentraxin I (NPTX1, Accession NM\_002522) is another VGAM447 host target gene. NPTX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NPTX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NPTX1 BINDING SITE, designated SEQ ID:8351, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21026] Another function of VGAM447 is therefore inhibition of Neuronal Pentraxin I (NPTX1, Accession NM\_002522), a gene which may be involved in synaptic uptake of extracellular material and is very strongly similar to rat NP1. Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with NPTX1. The function of NPTX1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM111.FLJ12057 (Accession NM\_024768) is another VGAM447 host target gene.

FLJ12057 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ12057, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12057 BINDING SITE, designated SEQ ID:24123, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21027] Another function of VGAM447 is therefore inhibition of FLJ12057 (Accession NM\_024768). Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12057. FLJ14075 (Accession NM\_024894) is another VGAM447 host target gene. FLJ14075 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14075, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14075 BINDING SITE, designated SEQ ID:24374, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21028] Another function of VGAM447 is therefore inhibition of FLJ14075 (Accession NM\_024894). Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14075. SCAM-1 (Accession NM\_005775) is another VGAM447 host target gene. SCAM-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCAM-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCAM-1 BINDING SITE, designated SEQ ID:12349, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21029] Another function of VGAM447 is therefore inhibition of SCAM-1 (Accession NM\_005775). Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCAM-1.



LOC138639 (Accession XM\_059988) is another VGAM447 host target gene. LOC138639 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC138639, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC138639 BINDING SITE, designated SEQ ID:37138, to the nucleotide sequence of VGAM447 RNA, herein designated VGAM RNA, also designated SEQ ID:3158.

[21030] Another function of VGAM447 is therefore inhibition of LOC138639 (Accession XM\_059988). Accordingly, utilities of VGAM447 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC138639. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 448 (VGAM448) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21031] VGAM448 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM448 was detected is described hereinabove with reference to Figs. 1–8.

[21032] VGAM448 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Papillomavirus Type 40. VGAM448 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21033] VGAM448 gene encodes a VGAM448 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM448 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM448 precursor RNA is designated SEQ ID:434, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:434 is located at position 2267 relative to the genome of Human Papillomavirus Type 40.

[21034] VGAM448 precursor RNA folds onto itself, forming VGAM448 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21035] An enzyme complex designated DICER COMPLEX, `dices` the VGAM448 folded precursor RNA into VGAM448 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 69%) nucleotide sequence of VGAM448 RNA is designated SEQ ID:3159, and is provided hereinbelow with reference to the sequence listing part.

[21036] VGAM448 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM448 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM448 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21037] VGAM448 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM448 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM448 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM448 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM448 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[21038] The complementary binding of VGAM448 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM448 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM448 host target RNA into VGAM448 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21039] It is appreciated that VGAM448 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM448 host target genes. The mRNA of each one of this plurality of VGAM448 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM448 RNA, herein designated VGAM RNA, and which when bound by VGAM448 RNA causes inhibition of translation of respective one or more VGAM448 host target proteins.

[21040] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM448 gene, herein designated VGAM GENE, on one or more VGAM448 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21041] It is yet further appreciated that a function of VGAM448 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM448 include diagnosis, prevention and treatment of viral infection by Human Papillomavirus Type 40. Specific functions, and accordingly utilities, of VGAM448 correlate with, and may be deduced from, the identity of the host target genes which VGAM448 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21042] Nucleotide sequences of the VGAM448 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM448 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM448 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM448 are further described hereinbelow with reference to Table 1.

[21043] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM448 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM448 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21044] As mentioned hereinabove with reference to Fig. 1, a function of VGAM448 gene, herein designated VGAM is inhibition of expression of VGAM448 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM448 correlate with, and may be deduced from, the identity of the target genes which VGAM448 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21045] G Protein-coupled Receptor 30 (GPR30, Accession NM\_001505) is a VGAM448 host target gene. GPR30 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GPR30, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR30 BINDING SITE, designated SEQ ID:7253, to the nucleotide sequence of VGAM448 RNA, herein designated VGAM RNA, also designated SEQ ID:3159.

[21046] A function of VGAM448 is therefore inhibition of G Protein-coupled Receptor 30 (GPR30, Accession NM\_001505), a gene which receives chemical signals in cell communication in both CNS and peripheral tissues. Accordingly, utilities of VGAM448 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR30. The function of GPR30 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM171.FLJ11273 (Accession NM\_018374) is another VGAM448 host target gene. FLJ11273 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11273 BINDING SITE, designated SEQ



ID:20393, to the nucleotide sequence of VGAM448 RNA, herein designated VGAM RNA, also designated SEQ ID:3159.

[21047] Another function of VGAM448 is therefore inhibition of FLJ11273 (Accession NM\_018374). Accordingly, utilities of VGAM448 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11273. FLJ12650 (Accession NM\_024522) is another VGAM448 host target gene. FLJ12650 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12650 BINDING SITE, designated SEQ ID:23721, to the nucleotide sequence of VGAM448 RNA, herein designated VGAM RNA, also designated SEQ ID:3159.

[21048] Another function of VGAM448 is therefore inhibition of FLJ12650 (Accession NM\_024522). Accordingly, utilities of VGAM448 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12650. KIAA0090 (Accession XM\_114045) is another VGAM448 host target gene. KIAA0090 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by KIAA0090, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0090 BINDING SITE, designated SEQ ID:42648, to the nucleotide sequence of VGAM448 RNA, herein designated VGAM RNA, also designated SEQ ID:3159.

[21049] Another function of VGAM448 is therefore inhibition of KIAA0090 (Accession XM\_114045). Accordingly, utilities of VGAM448 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0090. LOC124045 (Accession XM\_071873) is another VGAM448 host target gene. LOC124045 BINDING SITE1 through LOC124045 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC124045, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124045 BINDING SITE1 through LOC124045 BINDING SITE4, designated SEQ ID:37435, SEQ ID:37436, SEQ ID:37437 and SEQ ID:37438 respectively, to the nucleotide sequence of VGAM448

RNA, herein designated VGAM RNA, also designated SEQ ID:3159.

[21050] Another function of VGAM448 is therefore inhibition of LOC124045 (Accession XM\_071873). Accordingly, utilities of VGAM448 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124045. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 449 (VGAM449) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21051] VGAM449 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM449 was detected is described hereinabove with reference to Figs. 1–8.

[21052] VGAM449 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Papillomavirus Type 7. VGAM449 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21053] VGAM449 gene encodes a VGAM449 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM449 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM449 precursor RNA is designated SEQ ID:435, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:435 is located at position 5002 relative to the genome of Human Papillomavirus Type 7.

[21054] VGAM449 precursor RNA folds onto itself, forming VGAM449 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21055] An enzyme complex designated DICER COMPLEX, `dices` the VGAM449 folded precursor RNA into VGAM449 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 86%) nucleotide sequence of VGAM449 RNA is designated SEQ ID:3160, and is provided hereinbelow with reference to the sequence listing part.

[21056] VGAM449 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM449 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM449 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21057] VGAM449 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM449 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM449 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM449 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM449 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21058] The complementary binding of VGAM449 RNA, herein designated VGAM RNA, to host target binding sites on VGAM449 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM449 host target RNA into VGAM449 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21059] It is appreciated that VGAM449 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM449 host target genes. The mRNA of each one of this plurality of VGAM449 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM449 RNA, herein designated VGAM RNA, and which when bound by VGAM449 RNA causes inhibition of translation of respective one or more VGAM449 host target proteins.

[21060] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM449 gene, herein designated VGAM GENE, on one or more VGAM449 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[21061] It is yet further appreciated that a function of VGAM449 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of viral infection by Human Papillomavirus Type 7. Specific functions, and accordingly utilities, of VGAM449 correlate with, and may be deduced from, the identity of the host target genes which VGAM449 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21062] Nucleotide sequences of the VGAM449 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM449 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM449 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM449 are further described hereinbelow with reference to Table 1.

[21063] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM449 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM449 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21064] As mentioned hereinabove with reference to Fig. 1, a function of VGAM449 gene, herein designated VGAM is inhibition of expression of VGAM449 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM449 correlate with, and may be deduced from, the identity of the target genes which VGAM449 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21065] Acyl-Coenzyme A Dehydrogenase, Long Chain (ACADL, Accession NM\_001608) is a VGAM449 host target gene. ACADL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ACADL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACADL BINDING SITE, designated SEQ ID:7311, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21066] A function of VGAM449 is therefore inhibition of Acyl-

Coenzyme A Dehydrogenase, Long Chain (ACADL, Accession NM\_001608). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACADL. Potassium Voltage-gated Channel, Shal-related Subfamily, Member 2 (KCND2, Accession NM\_012281) is another VGAM449 host target gene. KCND2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCND2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCND2 BINDING SITE, designated SEQ ID:14606, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21067] Another function of VGAM449 is therefore inhibition of Potassium Voltage-gated Channel, Shal-related Subfamily, Member 2 (KCND2, Accession NM\_012281), a gene which is prominent in the repolarization phase of the action potential. Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCND2. The function of KCND2 has been established by previous studies. Kv4 (KCND)

proteins form voltage-activated A-type potassium ion channels and are prominent in the repolarization phase of the action potential. Zhu et al. (1999) cloned the cDNA encoding KCND2. The deduced 630-amino acid protein shares 99% sequence identity with the rat homolog and contains multiple potential phosphorylation sites as well as a membrane-spanning core region, including a P domain with the potassium channel signature GYGD, flanked by cytoplasmic hydrophilic N and C termini. Isbrandt et al. (2000) determined that KCND2 shares 60% identity and 71% homology with the KCND1 (OMIM Ref. No. 300281) and KCND3L (OMIM Ref. No. 605411) sequences, with the least conservation at the C terminus. By Northern blot analysis, Zhu et al. (1999) and Isbrandt et al. (2000) detected expression of a 6.8-kb transcript only in brain, particularly in the amygdala, caudate nucleus, cerebellum, hippocampus, substantia nigra, and thalamus. Heterologous expression determined that KCND2 mediates a rapidly inactivating, A-type outward potassium current which is not under the control of the N terminus as it is in Shaker channels (Zhu et al., 1999). Postma et al. (2000) resolved the intron-exon boundaries and flanking intron sequences of the KCND2 gene and found that it contains

6 exons. Zhu et al. (1999) mapped the KCND2 gene to chromosome 7q31–q32 by FISH. By radiation hybrid analysis, Postma et al. (2000) mapped the gene to 7q31

[21068] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21069] Isbrandt, D.; Leicher, T.; Waldschutz, R.; Zhu, X.; Luhmann, U.; Michel, U.; Sauter, K.; Pongs, O. : Gene structures and expression profiles of three human KCND (Kv4) potassium channels mediating A-type currents I(to) and I(sa). Genomics 64: 144–154, 2000. ; and

[21070] Postma, A. V.; Bezzina, C. R.; de Vries, J. F.; Wilde, A. A. M.; Moorman, A. F. M.; Mannens, M. M. A. M. : Genomic organisation and chromosomal localisation of two members of the KCND i.

[21071] Further studies establishing the function and utilities of KCND2 are found in John Hopkins OMIM database record ID 605410, and in cited publications numbered 10996–4783 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LNK (Accession NM\_005475) is another VGAM449 host target gene. LNK BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by

LNK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LNK BINDING SITE, designated SEQ ID:11969, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21072] Another function of VGAM449 is therefore inhibition of LNK (Accession NM\_005475), a gene which links T-cell receptor activation signal to phospholipase c-gamma-1, grb-2 and phosphatidylinositol 3-kinase (by similarity). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LNK. The function of LNK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM115. Retinoic Acid Receptor, Beta (RARβ, Accession NM\_000965) is another VGAM449 host target gene. RARβ BINDING SITE1 and RARβ BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RARβ, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of RARB BINDING SITE1 and RARB BINDING SITE2, designated SEQ ID:6694 and SEQ ID:18240 respectively, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21073] Another function of VGAM449 is therefore inhibition of Retinoic Acid Receptor, Beta (RARB, Accession NM\_000965), a gene which is one member of the steroid/thyroid hormone receptor family of ligand-activated transcription factors. Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RARB. The function of RARB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. Cyclin M1 (CNNM1, Accession NM\_020348) is another VGAM449 host target gene. CNNM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNNM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNNM1 BINDING SITE, designated SEQ ID:21609, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3160.

[21074] Another function of VGAM449 is therefore inhibition of Cyclin M1 (CNNM1, Accession NM\_020348). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNNM1. FLJ11181 (Accession NM\_018350) is another VGAM449 host target gene. FLJ11181 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ11181, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11181 BINDING SITE, designated SEQ ID:20363, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21075] Another function of VGAM449 is therefore inhibition of FLJ11181 (Accession NM\_018350). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11181. FLJ13576 (Accession NM\_022484) is another VGAM449 host target gene. FLJ13576 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ13576, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13576 BINDING SITE, designated SEQ ID:22862, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21076] Another function of VGAM449 is therefore inhibition of FLJ13576 (Accession NM\_022484). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13576. FLJ20079 (Accession NM\_017656) is another VGAM449 host target gene. FLJ20079 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20079, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20079 BINDING SITE, designated SEQ ID:19165, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21077] Another function of VGAM449 is therefore inhibition of FLJ20079 (Accession NM\_017656). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with FLJ20079. KIAA1163 (Accession XM\_086231) is another VGAM449 host target gene. KIAA1163 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1163, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1163 BINDING SITE, designated SEQ ID:38555, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21078] Another function of VGAM449 is therefore inhibition of KIAA1163 (Accession XM\_086231). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1163. KIAA1189 (Accession XM\_050508) is another VGAM449 host target gene. KIAA1189 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1189, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1189 BINDING SITE, designated SEQ ID:35649, to the

nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21079] Another function of VGAM449 is therefore inhibition of KIAA1189 (Accession XM\_050508). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1189. LOC148166 (Accession XM\_086077) is another VGAM449 host target gene. LOC148166 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC148166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148166 BINDING SITE, designated SEQ ID:38478, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21080] Another function of VGAM449 is therefore inhibition of LOC148166 (Accession XM\_086077). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148166. LOC150596 (Accession XM\_086957) is another VGAM449 host target gene. LOC150596 BINDING SITE is HOST TARGET binding site found in the 3` un-

translated region of mRNA encoded by LOC150596, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150596 BINDING SITE, designated SEQ ID:38994, to the nucleotide sequence of VGAM449 RNA, herein designated VGAM RNA, also designated SEQ ID:3160.

[21081] Another function of VGAM449 is therefore inhibition of LOC150596 (Accession XM\_086957). Accordingly, utilities of VGAM449 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150596. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 450 (VGAM450) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21082] VGAM450 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM450 was detected is described hereinabove with reference to Figs. 1–8.

[21083] VGAM450 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Cardamine Chlorotic Fleck Virus. VGAM450 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21084] VGAM450 gene encodes a VGAM450 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM450 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM450 precursor RNA is designated SEQ ID:436, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:436 is located at position 43 relative to the genome of Cardamine Chlorotic Fleck Virus.

[21085] VGAM450 precursor RNA folds onto itself, forming VGAM450 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21086] An enzyme complex designated DICER COMPLEX, `dices` the VGAM450 folded precursor RNA into VGAM450 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM450 RNA is designated SEQ ID:3161, and is provided hereinbelow with reference to the sequence listing part.

[21087] VGAM450 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM450 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM450 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21088] VGAM450 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM450 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM450 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM450 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM450 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21089] The complementary binding of VGAM450 RNA, herein designated VGAM RNA, to host target binding sites on VGAM450 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM450 host tar-

get RNA into VGAM450 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21090] It is appreciated that VGAM450 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM450 host target genes. The mRNA of each one of this plurality of VGAM450 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM450 RNA, herein designated VGAM RNA, and which when bound by VGAM450 RNA causes inhibition of translation of respective one or more VGAM450 host target proteins.

[21091] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM450 gene, herein designated VGAM GENE, on one or more VGAM450 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21092] It is yet further appreciated that a function of VGAM450 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM450 include diagnosis, prevention and treatment of viral infection by Cardamine Chlorotic Fleck Virus. Specific functions, and accordingly utilities, of VGAM450 correlate with, and may be deduced from, the identity of the host target genes which VGAM450 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21093] Nucleotide sequences of the VGAM450 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM450 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM450 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM450 are further



described hereinbelow with reference to Table 1.

[21094] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM450 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM450 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21095] As mentioned hereinabove with reference to Fig. 1, a function of VGAM450 gene, herein designated VGAM is inhibition of expression of VGAM450 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM450 correlate with, and may be deduced from, the identity of the target genes which VGAM450 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21096] Collagen, Type V, Alpha 1 (COL5A1, Accession NM\_000093) is a VGAM450 host target gene. COL5A1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by COL5A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of COL5A1 BINDING SITE, designated SEQ ID:5556, to the nucleotide sequence of VGAM450 RNA, herein designated VGAM RNA, also designated SEQ ID:3161.

[21097] A function of VGAM450 is therefore inhibition of Collagen, Type V, Alpha 1 (COL5A1, Accession NM\_000093). Accordingly, utilities of VGAM450 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COL5A1. Interleukin 2 Receptor, Beta (IL2RB, Accession NM\_000878) is another VGAM450 host target gene. IL2RB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL2RB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL2RB BINDING SITE, designated SEQ ID:6574, to the nucleotide sequence of VGAM450 RNA, herein designated VGAM RNA, also designated SEQ ID:3161.

[21098] Another function of VGAM450 is therefore inhibition of Interleukin 2 Receptor, Beta (IL2RB, Accession NM\_000878), a gene which is involved in receptor mediated endocytosis and transduces the mitogenic signals of il-2. Accordingly, utilities of VGAM450 include diagnosis,

prevention and treatment of diseases and clinical conditions associated with IL2RB. The function of IL2RB has been established by previous studies. Kondo et al. (2000) showed that a clonogenic common lymphoid progenitor, a bone marrow-resident cell that gives rise exclusively to lymphocytes (T, B, and natural killer cells), can be redirected to the myeloid lineage by stimulation through exogenously expressed interleukin-2 receptor and GM-CSF receptor (138981, 306250). Analysis of mutants of the beta chain of the IL2 receptor revealed that the granulocyte and monocyte differentiation signals are triggered by different cytoplasmic domains, showing that the signaling pathways responsible for these unique developmental outcomes are separable. Finally, Kondo et al. (2000) showed that the endogenous myelomonocytic cytokine receptors for GM-CSF and macrophage colony-stimulating factor (CSF1R; 164770) are expressed at low to moderate levels on the more primitive hematopoietic stem cells, are absent on common lymphoid progenitors, and are upregulated after myeloid lineage induction by IL2 (OMIM Ref. No. 147680). Kondo et al. (2000) concluded that cytokine signaling can regulate cell fate decisions and proposed that a critical step in lymphoid commitment is downregulation

lation of cytokine receptors that drive myeloid cell development Yang et al. (2001) analyzed T-cell subsets and levels of cytokine IL2 and soluble IL2 receptor in the peripheral blood of patients with normal pressure glaucoma (NPG; 606657) and primary open angle glaucoma (POAG; 137760) and compared them to age-matched controls. They found increased frequency of CD8<sup>+</sup>/HLA-DR<sup>+</sup> lymphocytes in patients with NPG and increased CD3<sup>+</sup>/CD8<sup>+</sup> lymphocytes in both NPG and POAG patients. CD5<sup>+</sup> lymphocytes were higher only in POAG patients. The mean concentration of soluble IL2R was higher in NPG and POAG patients than in controls although the IL2 concentration was similar in patients and controls. The authors concluded that the immune system might play an important role in initiation or progression of glaucomatous optic neuropathy in some patients Animal model experiments lend further support to the function of IL2RB. Suzuki et al. (1995) generated mice defective in Il2rb expression by insertion of a neomycin resistance cassette into the IL2RB gene at exon 6, which encodes a region of the extracellular domain proximal to the transmembrane region. Mice from 2 independent embryonic stem cell lines were separately bred homozygous for the defect, with both lineages

showing identical gross appearances. The mice showed normal growth until approximately 3 weeks after birth. After 4 weeks of age, they were generally smaller than normal or heterozygous littermates and had abnormal appearances characterized by fuzzy hair, slow movement, and fully developed external genitals. Death occurred at approximately 12 weeks. In mice lacking the IL2R beta chain, T cells were shown to be spontaneously activated, resulting in exhaustive differentiation of B cells into plasma cells and the appearance of high serum concentrations of immunoglobulins G1 and E, as well as autoantibodies that cause hemolytic anemia. Marked infiltrated granulocytopoiesis was also apparent. Depletion of CD4+ T cells in mutant mice rescued B cells without reversion of granulocyte abnormalities. T cells did not proliferate in response to polyclonal activators, nor could antigen-specific immune responses be elicited. Thus, Suzuki et al. (1995) concluded that Il2rb is required to keep the activation programs of T cells under control, to maintain homeostasis, and to prevent autoimmunity

[21099] It is appreciated that the abovementioned animal model for IL2RB is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appre-

ciated from the publications sited hereinbelow.

[21100] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21101] Kondo, M.; Scherer, D. C.; Miyamoto, T.; King, A. G.; Akashi, K.; Sugamura, K.; Weissman, I. L. : Cell-fate conversion of lymphoid-committed progenitors by instructive actions of cytokines. Nature 407: 383–386, 2000. ; and

[21102] Suzuki, H.; Kundig, T. M.; Furlonger, C.; Wakeham, A.; Timms, E.; Matsuyama, T.; Schmits, R.; Simard, J. J. L.; Ohashi, P. S.; Griesser, H.; Taniguchi, T.; Paige, C. J.; Mak, T. W. : De.

[21103] Further studies establishing the function and utilities of IL2RB are found in John Hopkins OMIM database record ID 146710, and in sited publications numbered 11979, 12006–12008, 4333, 12009–1201 and 386 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Nijmegen Breakage Syndrome 1 (nibrin) (NBS1, Accession XM\_045343) is another VGAM450 host target gene. NBS1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NBS1 BINDING SITE, designated SEQ ID:34438, to the nucleotide sequence of VGAM450 RNA, herein designated VGAM RNA, also designated SEQ ID:3161.

[21104] Another function of VGAM450 is therefore inhibition of Nijmegen Breakage Syndrome 1 (nibrin) (NBS1, Accession XM\_045343), a gene which may be involved in repair of DNA double-strand breaks. Accordingly, utilities of VGAM450 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NBS1. The function of NBS1 has been established by previous studies. Nijmegen breakage syndrome (NBS; 251260) is an autosomal recessive chromosomal instability syndrome characterized by microcephaly, growth retardation, immunodeficiency, and cancer predisposition. Cells from NBS patients are hypersensitive to ionizing radiation with cytogenetic features indistinguishable from those of ataxia-telangiectasia (AT; 208900). Varon et al. (1998) described the positional cloning of a gene encoding a novel protein, termed nibrin, that mapped within a 300-kb NBS critical interval on chromosome 8q21. The gene, designated NBS1, spans over 50 kb and contains 16

exons. Northern blot analysis revealed mRNA transcripts of 2.4 and 4.4 kb in all tissues examined. The predicted 754-amino acid protein contains 2 domains found in cell cycle checkpoint proteins, a forkhead-associated domain and an adjacent breast cancer carboxy-terminal domain. Varon et al. (1998) identified a truncating 5-bp deletion (602667.0001) in the majority of NBS patients studied, all of whom carried a conserved marker haplotype. Five additional truncating mutations were identified in patients with other distinct haplotypes. The domains found in nibrin and the NBS phenotype suggest that this disorder is caused by defective responses to DNA double-strand breaks (DSB). Animal model experiments lend further support to the function of NBS1. Zhu et al. (2001) generated mice deficient in NBS1 by targeted disruption. Nbs1  $-/-$  mice suffered early embryonic lethality and had poorly developed embryonic and extraembryonic tissues. Blastocysts showed greatly diminished expansion of the inner cell mass in culture, suggesting that NBS1 mediates essential functions during proliferation in the absence of externally induced damage. Zhu et al. (2001) concluded that the complex phenotypes observed in NBS patients and cell lines may not result from a complete inactivation



of NBS1 but may instead result from hypomorphic truncation mutations compatible with cell viability.

[21105] It is appreciated that the abovementioned animal model for NBS1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21106] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21107] Varon, R.; Vissinga, C.; Platzer, M.; Cerosaletti, K. M.; Chrzanowska, K. H.; Saar, K.; Beckmann, G.; Seemanova, E.; Cooper, P. R.; Nowak, N. J.; Stumm, M.; Weemaes, C. M. R.; Gatti, R. A.; Wilson, R. K.; Digweed, M.; Rosenthal, A.; Sperling, K.; Concannon, P.; Reis, A. : Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome. Cell 93: 467-476, 1998. ; and

[21108] Zhu, J.; Petersen, S.; Tessarollo, L.; Nussenzweig, A. : Targeted disruption of the Nijmegen breakage syndrome gene NBS1 leads to early embryonic lethality in mice. Curr. Biol. 11: 105-.

[21109] Further studies establishing the function and utilities of NBS1 are found in John Hopkins OMIM database record ID

602667, and in cited publications numbered 5918, 9233, 1551, 5919–5923, 9131, 8755–8756, 9438, 8757–8759, 714 and 8747 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Platelet-activating Factor Receptor (PTAFR, Accession NM\_000952) is another VGAM450 host target gene. PTAFR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTAFR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTAFR BINDING SITE, designated SEQ ID:6658, to the nucleotide sequence of VGAM450 RNA, herein designated VGAM RNA, also designated SEQ ID:3161.

[21110] Another function of VGAM450 is therefore inhibition of Platelet-activating Factor Receptor (PTAFR, Accession NM\_000952), a gene which is a platelet-activating factor receptor. Accordingly, utilities of VGAM450 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTAFR. The function of PTAFR has been established by previous studies. Platelet-activating factor (PAF) has been implicated as a mediator in diverse pathologic processes, such as allergy, asthma,

septic shock, arterial thrombosis, and inflammatory processes (Prescott et al., 1990). PAF is a phospholipid (1-O-alkyl-2-acetyl-sn-glycero-3-phosphorylcholine) and exerts its various effects via specific cell surface receptors that bind PAF with high affinity. Using a guinea pig probe, Seyfried et al. (1992) isolated the gene for human PAF receptor (PTAFR). The coding sequence contains no introns. The encoded protein is highly homologous to the guinea pig PAF receptor (82% identity) and contains 7 putative transmembrane domains. The PAF receptor therefore appears to be a member of the G protein-coupled family of receptors and exhibits significant similarity to many members of this family. By analysis of rodent/human somatic cell hybrids, Seyfried et al. (1992) concluded that the PTAFR gene is located on human chromosome 1. Chase et al. (1996) used fluorescence in situ hybridization to localize PTAFR to 1p35-p34.3.

[21111] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21112] Prescott, S. M.; Zimmerman, G. A.; McIntyre, T. M. : Platelet-activating factor. J. Biol. Chem. 265: 17381-17384, 1990. ; and

[21113] Seyfried, C. E.; Schweickart, V. L.; Godiska, R.; Gray, P. W. :  
The human platelet-activating factor receptor gene  
(PTAFR) contains no introns and maps to chromosome 1.  
Genomics 13: 832.

[21114] Further studies establishing the function and utilities of  
PTAFR are found in John Hopkins OMIM database record  
ID 173393, and in cited publications numbered  
3523–3525 listed in the bibliography section hereinbelow,  
which are also hereby incorporated by refer-  
ence. AF020591 (Accession NM\_014480) is another  
VGAM450 host target gene. AF020591 BINDING SITE is  
HOST TARGET binding site found in the 3` untranslated  
region of mRNA encoded by AF020591, corresponding to  
a HOST TARGET binding site such as BINDING SITE I,  
BINDING SITE II or BINDING SITE III. Table 2 illustrates the  
complementarity of the nucleotide sequences of  
AF020591 BINDING SITE, designated SEQ ID:15826, to the  
nucleotide sequence of VGAM450 RNA, herein designated  
VGAM RNA, also designated SEQ ID:3161.

[21115] Another function of VGAM450 is therefore inhibition of  
AF020591 (Accession NM\_014480). Accordingly, utilities  
of VGAM450 include diagnosis, prevention and treatment  
of diseases and clinical conditions associated with

AF020591. Inositol 1,3,4-triphosphate 5/6 Kinase (ITPK1, Accession NM\_014216) is another VGAM450 host target gene. ITPK1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ITPK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITPK1 BINDING SITE, designated SEQ ID:15481, to the nucleotide sequence of VGAM450 RNA, herein designated VGAM RNA, also designated SEQ ID:3161.

[21116] Another function of VGAM450 is therefore inhibition of Inositol 1,3,4-triphosphate 5/6 Kinase (ITPK1, Accession NM\_014216). Accordingly, utilities of VGAM450 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITPK1. Phosphodiesterase 4D Interacting Protein (myomegalin) (PDE4DIP, Accession NM\_014644) is another VGAM450 host target gene. PDE4DIP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PDE4DIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDE4DIP BINDING SITE, designated SEQ

ID:16052, to the nucleotide sequence of VGAM450 RNA, herein designated VGAM RNA, also designated SEQ ID:3161.

- [21117] Another function of VGAM450 is therefore inhibition of Phosphodiesterase 4D Interacting Protein (myomegalin) (PDE4DIP, Accession NM\_014644). Accordingly, utilities of VGAM450 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDE4DIP. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 451 (VGAM451) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [21118] VGAM451 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM451 was detected is described hereinabove with reference to Figs. 1–8.
- [21119] VGAM451 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cardamine Chlorotic Fleck Virus. VGAM451 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21120] VGAM451 gene encodes a VGAM451 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM451 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM451 precursor RNA is designated SEQ ID:437, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:437 is located at position 694 relative to the genome of Carmine Chlorotic Fleck Virus.

[21121] VGAM451 precursor RNA folds onto itself, forming VGAM451 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21122] An enzyme complex designated DICER COMPLEX, `dices` the VGAM451 folded precursor RNA into VGAM451 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM451 RNA is designated SEQ ID:3162, and is provided hereinbelow with reference to the sequence listing part.

[21123] VGAM451 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM451 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM451 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21124] VGAM451 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM451 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM451 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-



illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM451 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM451 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21125] The complementary binding of VGAM451 RNA, herein designated VGAM RNA, to host target binding sites on VGAM451 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM451 host target RNA into VGAM451 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21126] It is appreciated that VGAM451 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM451 host target genes. The mRNA of each one of this plurality of VGAM451 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM451 RNA, herein designated VGAM RNA, and which when bound by VGAM451 RNA causes inhibition of translation of respective one or more VGAM451 host target proteins.

[21127] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM451 gene, herein designated VGAM GENE, on one or more VGAM451 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[21128] It is yet further appreciated that a function of VGAM451 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM451 include diagnosis, prevention and treatment of viral infection by Cardamine Chlorotic Fleck Virus. Specific functions, and accordingly utilities, of VGAM451 correlate with, and may be deduced from, the identity of the host target genes which VGAM451 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21129] Nucleotide sequences of the VGAM451 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM451 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM451 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM451 are further described hereinbelow with reference to Table 1.

[21130] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM451 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM451 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21131] As mentioned hereinabove with reference to Fig. 1, a function of VGAM451 gene, herein designated VGAM is inhibition of expression of VGAM451 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM451 correlate with, and may be deduced from, the identity of the target genes which VGAM451 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21132] Diacylglycerol Kinase, Gamma 90kDa (DGKG, Accession NM\_001346) is a VGAM451 host target gene. DGKG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DGKG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGKG BINDING SITE, designated SEQ ID:7025, to the nucleotide sequence of VGAM451 RNA, herein designated VGAM RNA, also designated SEQ ID:3162.

[21133] A function of VGAM451 is therefore inhibition of Diacyl-

glycerol Kinase, Gamma 90kDa (DGKG, Accession NM\_001346), a gene which may convert diacylglycerol to phosphatidic acid. Accordingly, utilities of VGAM451 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DGKG. The function of DGKG has been established by previous studies. Kai et al. (1994) used degenerate PCR to clone a novel DGK, termed DGK-gamma, from HepG2 human hepatoma mRNA. They subsequently cloned a full-length cDNA from a HepG2 cDNA library. Sequence analysis revealed that DGK-gamma encodes a polypeptide of 791 amino acids which is 52% similar to that of DGK-alpha (DAGK1; 125855) and 62% similar to that of DGK-beta (OMIM Ref. No. 604070). All 3 DGK isozymes contain 2 conserved EF-hand calcium-binding motifs and 2 zinc finger domains. They also noted that some cDNAs contained a 25-amino acid truncation, which the authors presumed to be an alternate splicing variant. Both the full-length and truncated transcripts are present in a range of human tissues, with greatest expression observed in retina. When expressed in COS-7 cells, Kai et al. (1994) observed that full-length, but not truncated, DGK-gamma gave DGK activity. This activity was phosphatidylserine-dependent and had no

apparent specificity with regard to the acyl group. Kai et al. (1994) showed that DAGK3 is expressed predominantly in the human retina. Mutations in the gene encoding an eye-specific diacylglycerol kinase (DGK2) are known to cause retinal degeneration A (rdgA) in *Drosophila melanogaster* (Masai et al., 1993). Based on these findings, Stohr et al. (1999) reasoned that DAGK3 might be an excellent candidate gene for a human eye disease. They found that the human DAGK3 gene spans over 30 kb of genomic DNA interrupted by 23 introns. By FISH, they mapped the DAGK3 locus to 3q27–q28, overlapping the chromosomal region known to contain the gene (OPA1; 605290) underlying dominant optic atrophy (OMIM Ref. No. 165500), the most common form of hereditary atrophy of the optic nerve. Mutational analysis of the entire coding region of DAGK3 in 19 unrelated German optic atrophy-1 patients did not reveal any disease-causing mutations, thus excluding DAGK3 as a major cause underlying optic atrophy-1.

[21134] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21135] Kai, M.; Sakane, F.; Imai, S.; Wada, I.; Kanoh, H. : Molecular

cloning of a diacylglycerol kinase isozyme predominantly expressed in human retina with a truncated and inactive enzyme expression in most other human cells. J. Biol. Chem. 269: 18492–18498, 1994. ; and

[21136] Stohr, H.; Klein, J.; Gehrig, A.; Koehler, M. R.; Jurklies, B.; Kellner, U.; Leo-Kottler, B.; Schmid, M.; Weber, B. H. F. : Mapping and genomic characterization of the gene encoding diac.

[21137] Further studies establishing the function and utilities of DGKG are found in John Hopkins OMIM database record ID 601854, and in cited publications numbered 1266–1268 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ13955 (Accession NM\_024759) is another VGAM451 host target gene. FLJ13955 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13955, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13955 BINDING SITE, designated SEQ ID:24108, to the nucleotide sequence of VGAM451 RNA, herein designated VGAM RNA, also designated SEQ ID:3162.

[21138] Another function of VGAM451 is therefore inhibition of FLJ13955 (Accession NM\_024759). Accordingly, utilities of VGAM451 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13955. KIAA0356 (Accession XM\_038655) is another VGAM451 host target gene. KIAA0356 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0356, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0356 BINDING SITE, designated SEQ ID:32890, to the nucleotide sequence of VGAM451 RNA, herein designated VGAM RNA, also designated SEQ ID:3162.

[21139] Another function of VGAM451 is therefore inhibition of KIAA0356 (Accession XM\_038655). Accordingly, utilities of VGAM451 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0356. RASD Family, Member 2 (RASD2, Accession NM\_014310) is another VGAM451 host target gene. RASD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RASD2, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASD2 BINDING SITE, designated SEQ ID:15598, to the nucleotide sequence of VGAM451 RNA, herein designated VGAM RNA, also designated SEQ ID:3162.

[21140] Another function of VGAM451 is therefore inhibition of RASD Family, Member 2 (RASD2, Accession NM\_014310). Accordingly, utilities of VGAM451 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASD2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 452 (VGAM452) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21141] VGAM452 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM452 was detected is described hereinabove with reference to Figs. 1–8.

[21142] VGAM452 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cardamine Chlorotic

Fleck Virus. VGAM452 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21143] VGAM452 gene encodes a VGAM452 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM452 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM452 precursor RNA is designated SEQ ID:438, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:438 is located at position 2170 relative to the genome of Car-damine Chlorotic Fleck Virus.

[21144] VGAM452 precursor RNA folds onto itself, forming VGAM452 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21145] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM452 folded precursor RNA into VGAM452 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM452 RNA is designated SEQ ID:3163, and is provided hereinbelow with reference to the sequence listing part.

[21146] VGAM452 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM452 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM452 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21147] VGAM452 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM452 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM452 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM452 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM452 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[21148] The complementary binding of VGAM452 RNA, herein designated VGAM RNA, to host target binding sites on VGAM452 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM452 host target RNA into VGAM452 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21149] It is appreciated that VGAM452 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM452 host target genes. The mRNA of each one of this plurality of VGAM452 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM452 RNA, herein designated VGAM RNA, and which when bound by VGAM452 RNA causes inhibition of translation of respective one or more VGAM452 host target proteins.

[21150] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM452 gene, herein designated VGAM GENE, on one or more VGAM452 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21151] It is yet further appreciated that a function of VGAM452 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM452 include diagnosis, prevention and treatment of viral infection by Cardamine Chlorotic Fleck Virus. Specific functions, and accordingly utilities, of VGAM452 correlate with, and may be deduced from, the identity of the host target genes which VGAM452 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21152] Nucleotide sequences of the VGAM452 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM452 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM452 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM452 are further described hereinbelow with reference to Table 1.

- [21153] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM452 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM452 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21154] As mentioned hereinabove with reference to Fig. 1, a function of VGAM452 gene, herein designated VGAM is inhibition of expression of VGAM452 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM452 correlate with, and may be deduced from, the identity of the target genes which VGAM452 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [21155] TRIP15 (Accession NM\_004236) is a VGAM452 host target gene. TRIP15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIP15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIP15 BINDING SITE, designated SEQ ID:10430, to the nucleotide sequence of VGAM452 RNA,

herein designated VGAM RNA, also designated SEQ ID:3163.

[21156] A function of VGAM452 is therefore inhibition of TRIP15 (Accession NM\_004236), a gene which is a subunit of the COP9 signalosome complex. Accordingly, utilities of VGAM452 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIP15. The function of TRIP15 has been established by previous studies. TRIP15, or SGN2, is part of a 450-kD signalosome complex that includes COPS3 (OMIM Ref. No. 604665), COPS5 (OMIM Ref. No. 604850), GPS1 (OMIM Ref. No. 601934), and at least 4 other subunits. By autoradiographic analysis, Seeger et al. (1998) showed that the complex phosphorylates JUN (OMIM Ref. No. 165160), IKBA (OMIM Ref. No. 164008), and the C-terminal part of the p105 precursor of NFkB (OMIM Ref. No. 164011). The 26S proteasome is not a phosphorylation target, although immunofluorescence microscopy demonstrated that the 450-kD complex has a cytosolic localization, concentrated around the nucleus. Some nuclear hormone receptors (NHRs) silence gene expression in the absence of hormone. Corepressors, which are bound to the silencing domain of NHRs and are involved in the repression of



gene expression, dissociate upon hormone binding, leading to the binding of coactivators that mediate gene activation. TR is a transcriptional silencer in the absence of hormone as well as a hormone-dependent trans-activator, with its silencing domain localized in the C terminus.

Dressel et al. (1999) obtained a full-length HeLa cell cDNA encoding TRIP15, the human homolog of the *Drosophila* corepressor 'Alien.' Sequence analysis predicted that the 305-amino acid TRIP15 protein, which is 90% identical and 95% similar to *Drosophila* Alien, contains an acidic region in the N terminus, a putative zinc finger in the C terminus, and a central hydrophobic core region flanked by 2 putative alpha-helical structures and a nuclear localization signal. Western blot analysis determined that TRIP15 is expressed as a 41-kD protein. Yeast 2-hybrid, GST pull-down, and coimmunoprecipitation analyses showed that TRIP15 interacts with the C terminus of TR, but not with intact RAR (OMIM Ref. No. 180240), only in the absence of hormone. Immunofluorescence microscopy demonstrated that TRIP15 is localized in the nucleus. Reporter assays indicated that TRIP15 increases receptor-mediated silencing and harbors an autonomous silencing function, which correlates with the ability of TRIP15 to interact with TR in

both the hinge region and the C-terminal end of the TR silencing domain.

[21157] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21158] Seeger, M.; Kraft, R.; Ferrell, K.; Dawadschargal, B.-O.; Dumdey, R.; Schade, R.; Gordon, C.; Naumann, M.; Dubiel, W. : A novel protein complex involved in signal transduction possessing similarities to 26S proteasome subunits. FASEB J. 12: 469-478, 1998. ; and

[21159] Dressel, U.; Thormeyer, D.; Altincicek, B.; Paululat, A.; Egger, M.; Schneider, S.; Tenbaum, S. P.; Renkawitz, R.; Baniahmad, A. : Alien, a highly conserved protein with characteristics of.

[21160] Further studies establishing the function and utilities of TRIP15 are found in John Hopkins OMIM database record ID 604508, and in cited publications numbered 544 and 6199-5445 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ10901 (Accession NM\_018265) is another VGAM452 host target gene. FLJ10901 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10901, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10901 BINDING SITE, designated SEQ ID:20234, to the nucleotide sequence of VGAM452 RNA, herein designated VGAM RNA, also designated SEQ ID:3163.

[21161] Another function of VGAM452 is therefore inhibition of FLJ10901 (Accession NM\_018265). Accordingly, utilities of VGAM452 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10901. GW112 (Accession NM\_006418) is another VGAM452 host target gene. GW112 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GW112, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GW112 BINDING SITE, designated SEQ ID:13133, to the nucleotide sequence of VGAM452 RNA, herein designated VGAM RNA, also designated SEQ ID:3163.

[21162] Another function of VGAM452 is therefore inhibition of GW112 (Accession NM\_006418). Accordingly, utilities of VGAM452 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with GW112. KIAA0976 (Accession NM\_014917) is another VGAM452 host target gene. KIAA0976 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0976, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0976 BINDING SITE, designated SEQ ID:17166, to the nucleotide sequence of VGAM452 RNA, herein designated VGAM RNA, also designated SEQ ID:3163.

[21163] Another function of VGAM452 is therefore inhibition of KIAA0976 (Accession NM\_014917). Accordingly, utilities of VGAM452 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0976. LOC245771 (Accession XM\_167366) is another VGAM452 host target gene. LOC245771 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC245771, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC245771 BINDING SITE, designated SEQ ID:44639, to

the nucleotide sequence of VGAM452 RNA, herein designated VGAM RNA, also designated SEQ ID:3163.

[21164] Another function of VGAM452 is therefore inhibition of LOC245771 (Accession XM\_167366). Accordingly, utilities of VGAM452 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC245771. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 453 (VGAM453) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21165] VGAM453 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM453 was detected is described hereinabove with reference to Figs. 1–8.

[21166] VGAM453 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Borna Disease Virus. VGAM453 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21167] VGAM453 gene encodes a VGAM453 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM453 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM453 precursor RNA is designated SEQ ID:439, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:439 is located at position 5441 relative to the genome of Borna Disease Virus.

[21168] VGAM453 precursor RNA folds onto itself, forming VGAM453 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21169] An enzyme complex designated DICER COMPLEX, `dices` the VGAM453 folded precursor RNA into VGAM453 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM453 RNA is designated SEQ ID:3164, and is provided hereinbelow with reference to the sequence listing part.

[21170] VGAM453 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM453 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM453 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[21171] VGAM453 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM453 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM453 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM453 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM453 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21172] The complementary binding of VGAM453 RNA, herein designated VGAM RNA, to host target binding sites on VGAM453 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM453 host target RNA into VGAM453 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21173] It is appreciated that VGAM453 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents



a plurality of VGAM453 host target genes. The mRNA of each one of this plurality of VGAM453 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM453 RNA, herein designated VGAM RNA, and which when bound by VGAM453 RNA causes inhibition of translation of respective one or more VGAM453 host target proteins.

[21174] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM453 gene, herein designated VGAM GENE, on one or more VGAM453 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[21175] It is yet further appreciated that a function of VGAM453 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM453 include diagnosis, prevention and treatment of viral infection by Borna Disease Virus. Specific functions, and accordingly utilities, of VGAM453 correlate with, and may be deduced from, the identity of the host target genes which VGAM453 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21176] Nucleotide sequences of the VGAM453 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM453 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM453 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM453 are further described hereinbelow with reference to Table 1.

[21177] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM453 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM453 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21178] As mentioned hereinabove with reference to Fig. 1, a function of VGAM453 gene, herein designated VGAM is inhibition of expression of VGAM453 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM453 correlate with, and may be deduced from, the identity of the target genes which VGAM453 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21179] Aldehyde Dehydrogenase 3 Family, Member B2 (ALDH3B2, Accession NM\_000695) is a VGAM453 host target gene. ALDH3B2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALDH3B2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALDH3B2 BINDING SITE, designated SEQ ID:6355, to the nucleotide sequence of VGAM453 RNA, herein designated VGAM RNA, also designated SEQ ID:3164.

[21180] A function of VGAM453 is therefore inhibition of Aldehyde

Dehydrogenase 3 Family, Member B2 (ALDH3B2, Accession NM\_000695), a gene which may play a role in alcohol detoxitation. Accordingly, utilities of VGAM453 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALDH3B2. The function of ALDH3B2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM251.FLJ20813 (Accession NM\_017961) is another VGAM453 host target gene. FLJ20813 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20813, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20813 BINDING SITE, designated SEQ ID:19677, to the nucleotide sequence of VGAM453 RNA, herein designated VGAM RNA, also designated SEQ ID:3164.

[21181] Another function of VGAM453 is therefore inhibition of FLJ20813 (Accession NM\_017961). Accordingly, utilities of VGAM453 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20813. LOC149650 (Accession XM\_086623) is another VGAM453

host target gene. LOC149650 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149650 BINDING SITE, designated SEQ ID:38795, to the nucleotide sequence of VGAM453 RNA, herein designated VGAM RNA, also designated SEQ ID:3164.

[21182] Another function of VGAM453 is therefore inhibition of LOC149650 (Accession XM\_086623). Accordingly, utilities of VGAM453 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149650. LOC150397 (Accession XM\_086907) is another VGAM453 host target gene. LOC150397 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150397 BINDING SITE, designated SEQ ID:38958, to the nucleotide sequence of VGAM453 RNA, herein designated VGAM RNA, also designated SEQ ID:3164.

[21183] Another function of VGAM453 is therefore inhibition of LOC150397 (Accession XM\_086907). Accordingly, utilities of VGAM453 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150397. LOC161823 (Accession XM\_091156) is another VGAM453 host target gene. LOC161823 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC161823, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161823 BINDING SITE, designated SEQ ID:40029, to the nucleotide sequence of VGAM453 RNA, herein designated VGAM RNA, also designated SEQ ID:3164.

[21184] Another function of VGAM453 is therefore inhibition of LOC161823 (Accession XM\_091156). Accordingly, utilities of VGAM453 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161823. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 454 (VGAM454) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[21185] VGAM454 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM454 was detected is described hereinabove with reference to Figs. 1–8.

[21186] VGAM454 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Borna Disease Virus. VGAM454 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21187] VGAM454 gene encodes a VGAM454 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM454 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM454 precursor RNA is designated SEQ ID:440, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:440 is located at position 8313 relative to the genome of Borna Disease Virus.

[21188] VGAM454 precursor RNA folds onto itself, forming VGAM454 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[21189] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM454 folded precursor RNA into VGAM454 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 81%) nucleotide se-  
quence of VGAM454 RNA is designated SEQ ID:3165, and  
is provided hereinbelow with reference to the sequence  
listing part.

[21190] VGAM454 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM454 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM454 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding



gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21191] VGAM454 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM454 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM454 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM454 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM454 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21192] The complementary binding of VGAM454 RNA, herein designated VGAM RNA, to host target binding sites on VGAM454 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM454 host target RNA into VGAM454 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21193] It is appreciated that VGAM454 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM454 host target genes. The mRNA of each one of this plurality of VGAM454 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM454 RNA, herein designated VGAM RNA, and which when bound by VGAM454 RNA causes inhibition of translation of respective one or more VGAM454 host target proteins.

[21194] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM454 gene, herein designated VGAM GENE, on one or more VGAM454 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21195] It is yet further appreciated that a function of VGAM454 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM454 include diagnosis, prevention and treatment of viral infection by Borna Disease Virus. Specific functions, and accordingly utilities, of VGAM454 correlate with, and may be deduced from, the identity of the host target genes which VGAM454 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

- [21196] Nucleotide sequences of the VGAM454 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM454 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM454 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM454 are further described hereinbelow with reference to Table 1.
- [21197] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM454 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM454 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21198] As mentioned hereinabove with reference to Fig. 1, a function of VGAM454 gene, herein designated VGAM is inhibition of expression of VGAM454 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM454 correlate with, and may be deduced from, the identity of the target genes which VGAM454 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21199] LNK (Accession NM\_005475) is a VGAM454 host target gene. LNK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LNK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LNK BINDING SITE, designated SEQ ID:11971, to the nucleotide sequence of VGAM454 RNA, herein designated VGAM RNA, also designated SEQ ID:3165.

[21200] A function of VGAM454 is therefore inhibition of LNK (Accession NM\_005475), a gene which links T-cell receptor activation signal to phospholipase c-gamma-1, grb-2 and phosphatidylinositol 3-kinase (by similarity). Accordingly, utilities of VGAM454 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LNK. The function of LNK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM115.KIAA0265 (Accession XM\_045954) is another VGAM454 host target gene. KIAA0265 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0265, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0265 BINDING SITE, designated SEQ ID:34618, to the nucleotide sequence of VGAM454 RNA, herein designated VGAM RNA, also designated SEQ ID:3165.

[21201] Another function of VGAM454 is therefore inhibition of KIAA0265 (Accession XM\_045954). Accordingly, utilities of VGAM454 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0265. KIAA0960 (Accession XM\_166543) is another VGAM454 host target gene. KIAA0960 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0960, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0960 BINDING SITE, designated SEQ ID:44519, to the nucleotide sequence of VGAM454 RNA, herein designated VGAM RNA, also designated SEQ ID:3165.

[21202] Another function of VGAM454 is therefore inhibition of KIAA0960 (Accession XM\_166543). Accordingly, utilities of VGAM454 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0960. LOC138428 (Accession XM\_059972) is another VGAM454 host target gene. LOC138428 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC138428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC138428 BINDING SITE, designated SEQ ID:37133, to the nucleotide sequence of VGAM454 RNA, herein designated VGAM RNA, also designated SEQ ID:3165.

[21203] Another function of VGAM454 is therefore inhibition of LOC138428 (Accession XM\_059972). Accordingly, utilities of VGAM454 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC138428. LOC152048 (Accession XM\_098158) is another VGAM454 host target gene. LOC152048 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC152048, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152048 BINDING SITE, designated SEQ ID:41427, to

the nucleotide sequence of VGAM454 RNA, herein designated VGAM RNA, also designated SEQ ID:3165.

[21204] Another function of VGAM454 is therefore inhibition of LOC152048 (Accession XM\_098158). Accordingly, utilities of VGAM454 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152048. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 455 (VGAM455) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21205] VGAM455 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM455 was detected is described hereinabove with reference to Figs. 1–8.

[21206] VGAM455 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Borna Disease Virus. VGAM455 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21207] VGAM455 gene encodes a VGAM455 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM455 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM455 precursor RNA is designated SEQ ID:441, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:441 is located at position 5801 relative to the genome of Borna Disease Virus.

[21208] VGAM455 precursor RNA folds onto itself, forming VGAM455 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21209] An enzyme complex designated DICER COMPLEX, `dices` the VGAM455 folded precursor RNA into VGAM455 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM455 RNA is designated SEQ ID:3166, and is provided hereinbelow with reference to the sequence listing part.

[21210] VGAM455 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM455 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM455 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[21211] VGAM455 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM455 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM455 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM455 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM455 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21212] The complementary binding of VGAM455 RNA, herein designated VGAM RNA, to host target binding sites on VGAM455 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM455 host target RNA into VGAM455 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21213] It is appreciated that VGAM455 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM455 host target genes. The mRNA of each one of this plurality of VGAM455 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM455 RNA, herein designated VGAM RNA, and which when bound by VGAM455 RNA causes inhibition of translation of respective one or more VGAM455 host target proteins.

[21214] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM455 gene, herein designated VGAM GENE, on one or more VGAM455 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[21215] It is yet further appreciated that a function of VGAM455 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM455 include diagnosis, prevention and treatment of viral infection by Borna Disease Virus. Specific functions, and accordingly utilities, of VGAM455 correlate with, and may be deduced from, the identity of the host target genes which VGAM455 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21216] Nucleotide sequences of the VGAM455 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM455 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM455 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM455 are further described hereinbelow with reference to Table 1.

[21217] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM455 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM455 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21218] As mentioned hereinabove with reference to Fig. 1, a function of VGAM455 gene, herein designated VGAM is inhibition of expression of VGAM455 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM455 correlate with, and may be deduced from, the identity of the target genes which VGAM455 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21219] EphB3 (EPHB3, Accession NM\_004443) is a VGAM455 host target gene. EPHB3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPHB3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPHB3 BINDING SITE, designated SEQ ID:10737, to the nucleotide sequence of VGAM455 RNA, herein designated VGAM RNA, also designated SEQ ID:3166.

[21220] A function of VGAM455 is therefore inhibition of EphB3 (EPHB3, Accession NM\_004443), a gene which receptor for

members of the ephrin-b family. binds to ephrin-b1 and -b2. Accordingly, utilities of VGAM455 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPHB3. The function of EPHB3 has been established by previous studies. See 179610 for background on Eph receptors and their ligands, the ephrins. Bohme et al. (1993) used PCR to isolate a novel protein tyrosine kinase (PTK), which they termed HEK2 for 'human embryo kinase-2,' from a human embryonic cDNA library. Sequence analysis revealed that HEK2 encodes a 998-amino acid polypeptide having a single putative transmembrane domain, a secretory signal sequence, and 2 fibronectin repeats. Based on sequence homology, Bohme et al. (1993) stated that HEK2 is a member of the EPH/ELK family of tyrosine kinases. Northern blot analysis revealed that HEK2 was expressed as a variable 4.6-kb message in all adult human tissues tested. Southern blot analysis suggested that HEK2 is a single-copy gene in the human genome. Bohme et al. (1993) used PCR of human-mouse hybrids to map the HEK2 gene to human chromosome 3q21-qter. Bohme et al. (1996) presented evidence that HEK2 interacts with 2 ligands of EPH-related kinases (LERKs), namely, LERK2 (EFNB1; 300035) and LERK5

(EFNB2; 600527). They reported that coincubation of HEK2- and LERK2-expressing cells induces cell-cell adhesion and aggregation. Additionally, coexpression of HEK2 and LERK2 results in reduced kinase activity of HEK2. Halford et al. (2000) generated mice deficient in Ryk (OMIM Ref. No. 600524) and found that they had a distinctive craniofacial appearance, shortened limbs, and postnatal mortality due to feeding and respiratory complications associated with a complete cleft of the secondary palate. Consistent with cleft palate phenocopy in Ephb2 (OMIM Ref. No. 600997)/Ephb3-deficient mice and the role of a Drosophila Ryk ortholog, 'Derailed,' in the transduction of repulsive axon pathfinding cues, biochemical data implicated Ryk in signaling mediated by Eph receptors and cell junction-associated Af6 (OMIM Ref. No. 159559). Halford et al. (2000) concluded that their findings highlighted the importance of signal crosstalk between members of different RTK subfamilies.

[21221] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21222] Bohme, B.; Holtrich, U.; Wolf, G.; Luzius, H.; Grzeschik, K.-H.; Strebhardt, K.; Rubsamen-Waigmann, H. : PCR me-



diated detection of a new human receptor-tyrosine-kinase, HEK 2. Oncogene 8: 2857-2862, 1993. ; and

[21223] Halford, M. M.; Armes, J.; Buchert, M.; Meskenaite, V.; Grail, D.; Hibbs, M. L.; Wilks, A. F.; Farlie, P. G.; Newgreen, D. F.; Hovens, C. M.; Stacker, S. A. : Ryk-deficient mice exhibit.

[21224] Further studies establishing the function and utilities of EPHB3 are found in John Hopkins OMIM database record ID 601839, and in cited publications numbered 887 and 8879 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0222 (Accession NM\_014643) is another VGAM455 host target gene. KIAA0222 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0222, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0222 BINDING SITE, designated SEQ ID:16045, to the nucleotide sequence of VGAM455 RNA, herein designated VGAM RNA, also designated SEQ ID:3166.

[21225] Another function of VGAM455 is therefore inhibition of KIAA0222 (Accession NM\_014643). Accordingly, utilities

of VGAM455 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0222. MGC10818 (Accession NM\_030568) is another VGAM455 host target gene. MGC10818 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC10818, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC10818 BINDING SITE, designated SEQ ID:24943, to the nucleotide sequence of VGAM455 RNA, herein designated VGAM RNA, also designated SEQ ID:3166.

[21226] Another function of VGAM455 is therefore inhibition of MGC10818 (Accession NM\_030568). Accordingly, utilities of VGAM455 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10818. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 456 (VGAM456) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21227] VGAM456 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM456 was detected is described hereinabove with reference to Figs. 1–8.

[21228] VGAM456 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM456 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21229] VGAM456 gene encodes a VGAM456 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM456 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM456 precursor RNA is designated SEQ ID:442, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:442 is located at position 31089 relative to the genome of Variola Virus.

[21230] VGAM456 precursor RNA folds onto itself, forming VGAM456 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21231] An enzyme complex designated DICER COMPLEX, `dices` the VGAM456 folded precursor RNA into VGAM456 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM456 RNA is designated SEQ ID:3167, and is provided hereinbelow with reference to the sequence listing part.

[21232] VGAM456 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM456 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM456 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21233] VGAM456 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM456 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM456 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM456 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM456 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21234] The complementary binding of VGAM456 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM456 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM456 host target RNA into VGAM456 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21235] It is appreciated that VGAM456 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM456 host target genes. The mRNA of each one of this plurality of VGAM456 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM456 RNA, herein designated VGAM RNA, and which when bound by VGAM456 RNA causes inhibition of translation of respective one or more VGAM456 host target proteins.

[21236] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM456 gene, herein designated VGAM GENE, on one or more VGAM456 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21237] It is yet further appreciated that a function of VGAM456 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM456 include diagnosis, prevention and treatment of viral infection by Variola Virus. Specific functions, and accordingly utilities, of VGAM456 correlate with, and may be deduced from, the identity of the host target genes which VGAM456 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21238] Nucleotide sequences of the VGAM456 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM456 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM456 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM456 are further described hereinbelow with reference to Table 1.

[21239] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM456 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM456 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21240] As mentioned hereinabove with reference to Fig. 1, a function of VGAM456 gene, herein designated VGAM is inhibition of expression of VGAM456 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM456 correlate with, and may be deduced from, the identity of the target genes which VGAM456 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21241] Regulator of G-protein Signalling 17 (RGS17, Accession NM\_012419) is a VGAM456 host target gene. RGS17 BINDING SITE is HOST TARGET binding site found in the



3' untranslated region of mRNA encoded by RGS17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RGS17 BINDING SITE, designated SEQ ID:14791, to the nucleotide sequence of VGAM456 RNA, herein designated VGAM RNA, also designated SEQ ID:3167.

[21242] A function of VGAM456 is therefore inhibition of Regulator of G-protein Signalling 17 (RGS17, Accession NM\_012419). Accordingly, utilities of VGAM456 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RGS17. Zinc Finger Protein 387 (ZNF387, Accession NM\_014682) is another VGAM456 host target gene. ZNF387 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF387, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF387 BINDING SITE, designated SEQ ID:16172, to the nucleotide sequence of VGAM456 RNA, herein designated VGAM RNA, also designated SEQ ID:3167.

[21243] Another function of VGAM456 is therefore inhibition of

Zinc Finger Protein 387 (ZNF387, Accession NM\_014682). Accordingly, utilities of VGAM456 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF387. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 457 (VGAM457) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21244] VGAM457 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM457 was detected is described hereinabove with reference to Figs. 1–8.

[21245] VGAM457 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM457 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21246] VGAM457 gene encodes a VGAM457 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM457 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM457 precursor RNA is designated SEQ ID:443, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:443 is located at position 31432 relative to the genome of Vari-ola Virus.

[21247] VGAM457 precursor RNA folds onto itself, forming VGAM457 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21248] An enzyme complex designated DICER COMPLEX, `dices` the VGAM457 folded precursor RNA into VGAM457 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM457 RNA is designated SEQ ID:3168, and

is provided hereinbelow with reference to the sequence listing part.

[21249] VGAM457 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM457 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM457 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21250] VGAM457 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM457 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM457 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM457 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM457 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21251] The complementary binding of VGAM457 RNA, herein designated VGAM RNA, to host target binding sites on VGAM457 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM457 host target RNA into VGAM457 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21252] It is appreciated that VGAM457 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM457 host target genes. The mRNA of each one of this plurality of VGAM457 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM457 RNA, herein designated VGAM RNA, and which when bound by VGAM457 RNA causes inhibition of translation of respective one or more VGAM457 host target proteins.

[21253] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM457 gene, herein designated VGAM GENE, on one or more VGAM457 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21254] It is yet further appreciated that a function of VGAM457 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM457 include diagnosis, prevention and treatment of viral infection by Variola Virus. Specific functions, and accordingly utilities, of VGAM457 correlate with, and may be deduced from, the identity of the host target genes which VGAM457 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21255] Nucleotide sequences of the VGAM457 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM457 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM457 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM457 are further described hereinbelow with reference to Table 1.

[21256] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM457 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM457 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21257] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM457 gene, herein designated VGAM is inhibition of expression of VGAM457 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM457 correlate with, and may be deduced from, the identity of the target genes which VGAM457 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21258] Calsequestrin 2 (cardiac muscle) (CASQ2, Accession NM\_001232) is a VGAM457 host target gene. CASQ2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CASQ2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CASQ2 BINDING SITE, designated SEQ ID:6903, to the nucleotide sequence of VGAM457 RNA, herein designated VGAM RNA, also designated SEQ ID:3168.

[21259] A function of VGAM457 is therefore inhibition of Calsequestrin 2 (cardiac muscle) (CASQ2, Accession NM\_001232). Accordingly, utilities of VGAM457 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CASQ2. KIAA1715 (Accession XM\_042834) is another VGAM457 host target



gene. KIAA1715 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1715, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1715 BINDING SITE, designated SEQ ID:33792, to the nucleotide sequence of VGAM457 RNA, herein designated VGAM RNA, also designated SEQ ID:3168.

[21260] Another function of VGAM457 is therefore inhibition of KIAA1715 (Accession XM\_042834). Accordingly, utilities of VGAM457 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1715. PRO0097 (Accession NM\_014114) is another VGAM457 host target gene. PRO0097 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO0097, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0097 BINDING SITE, designated SEQ ID:15365, to the nucleotide sequence of VGAM457 RNA, herein designated VGAM RNA, also designated SEQ ID:3168.

[21261] Another function of VGAM457 is therefore inhibition of PRO0097 (Accession NM\_014114). Accordingly, utilities of VGAM457 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0097. LOC143915 (Accession XM\_096502) is another VGAM457 host target gene. LOC143915 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143915, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143915 BINDING SITE, designated SEQ ID:40380, to the nucleotide sequence of VGAM457 RNA, herein designated VGAM RNA, also designated SEQ ID:3168.

[21262] Another function of VGAM457 is therefore inhibition of LOC143915 (Accession XM\_096502). Accordingly, utilities of VGAM457 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143915. LOC170063 (Accession XM\_104820) is another VGAM457 host target gene. LOC170063 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC170063, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170063 BINDING SITE, designated SEQ ID:42188, to the nucleotide sequence of VGAM457 RNA, herein designated VGAM RNA, also designated SEQ ID:3168.

[21263] Another function of VGAM457 is therefore inhibition of LOC170063 (Accession XM\_104820). Accordingly, utilities of VGAM457 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170063. LOC90268 (Accession XM\_030424) is another VGAM457 host target gene. LOC90268 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90268 BINDING SITE, designated SEQ ID:31041, to the nucleotide sequence of VGAM457 RNA, herein designated VGAM RNA, also designated SEQ ID:3168.

[21264] Another function of VGAM457 is therefore inhibition of LOC90268 (Accession XM\_030424). Accordingly, utilities of VGAM457 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC90268. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 458 (VGAM458) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21265] VGAM458 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM458 was detected is described hereinabove with reference to Figs. 1–8.

[21266] VGAM458 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Camelpox Virus. VGAM458 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21267] VGAM458 gene encodes a VGAM458 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM458 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM458 precursor RNA is designated SEQ ID:444, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:444 is located at position 72676 relative to the genome of Camelpox Virus.

[21268] VGAM458 precursor RNA folds onto itself, forming VGAM458 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21269] An enzyme complex designated DICER COMPLEX, `dices` the VGAM458 folded precursor RNA into VGAM458 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM458 RNA is designated SEQ ID:3169, and is provided hereinbelow with reference to the sequence listing part.

[21270] VGAM458 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM458 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM458 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21271] VGAM458 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM458 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM458 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM458 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM458 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[21272] The complementary binding of VGAM458 RNA, herein designated VGAM RNA, to host target binding sites on VGAM458 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM458 host target RNA into VGAM458 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21273] It is appreciated that VGAM458 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM458 host target genes. The mRNA of each one of this plurality of VGAM458 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM458 RNA, herein designated VGAM RNA, and which when bound by VGAM458 RNA causes in-

hibition of translation of respective one or more VGAM458 host target proteins.

[21274] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM458 gene, herein designated VGAM GENE, on one or more VGAM458 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21275] It is yet further appreciated that a function of VGAM458 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM458 include diagnosis, prevention and



treatment of viral infection by Camelpox Virus. Specific functions, and accordingly utilities, of VGAM458 correlate with, and may be deduced from, the identity of the host target genes which VGAM458 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [21276] Nucleotide sequences of the VGAM458 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM458 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM458 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM458 are further described hereinbelow with reference to Table 1.
- [21277] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM458 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM458 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21278] As mentioned hereinabove with reference to Fig. 1, a function of VGAM458 gene, herein designated VGAM is inhibition of expression of VGAM458 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM458 correlate with, and may be deduced from, the identity of the target genes which VGAM458 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21279] Hydroxysteroid (17-beta) Dehydrogenase 1 (HSD17B1, Accession NM\_000413) is a VGAM458 host target gene. HSD17B1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HSD17B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSD17B1 BINDING SITE, designated SEQ ID:5996, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21280] A function of VGAM458 is therefore inhibition of Hydroxysteroid (17-beta) Dehydrogenase 1 (HSD17B1, Accession NM\_000413). Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSD17B1. Integral Membrane Protein 2B (ITM2B, Accession NM\_021999) is another VGAM458 host target gene. ITM2B BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITM2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITM2B BINDING SITE, designated SEQ ID:22541, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21281] Another function of VGAM458 is therefore inhibition of Integral Membrane Protein 2B (ITM2B, Accession NM\_021999), a gene which is a member of the type II integral membrane protein family. Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITM2B. The function of ITM2B has been established by previous studies. Using isolated amyloid fibrils from a patient with familial British dementia (FBD; 176500), Vidal et al. (1999) identified a unique 4-kD protein subunit, which they called ABRI, that is encoded by a novel gene, BRI. The BRI cDNA encodes a predicted protein of 266 amino acids. The first ATG is located 150 basepairs downstream of an in-frame TAG stop codon and has a classic Kozak consensus sequence. Hydropathy analysis indicated the presence

of a putative single transmembrane-spanning domain between amino acids 52 and 74, indicating that this highly insoluble molecule is a type II integral transmembrane protein with the C-terminal part being extracellular. A potential N-glycosylation site was identified at asparagine-170. Homology searches done with other species including chicken, rat, mouse, rabbit, and pig showed highly homologous ORFs, with human and murine identity being 96%. Northern blot analysis revealed 2.0- and 1.6-kb mRNA transcripts, which were expressed in most regions of the brain as well as in several peripheral tissues Ghiso et al. (2001) reported that carriers of the ter267-to-arg mutation (603904.0001) have a soluble form of the amyloid peptide (sABRI) in the circulation with an estimated concentration in the range of 20 ng/ml, several-fold higher than that of soluble amyloid-beta (OMIM Ref. No. 104760). In addition, ABRI species identical to those identified in the brain were also found as fibrillar components of amyloid deposits predominantly in the blood vessels of several peripheral tissues, including pancreas and myocardium. Ghiso et al. (2001) hypothesized that the high concentration of the soluble de novo-created amyloidal peptide and/or the insufficient tissue clearance are

the main causative factors for the formation of amyloid deposits outside the brain. Thus, familial British dementia constitutes the first documented cerebral amyloidosis associated with neurodegeneration and dementia in which the amyloid deposition is also systemic

[21282] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21283] Ghiso, J. A.; Holton, J.; Miravalle, L.; Calero, M.; Lashley, T.; Vidal, R.; Houlden, H.; Wood, N.; Neubert, T. A.; Rostagno, A.; Plant, G.; Revesz, T.; Frangione, B. : Systemic amyloid deposits in familial British dementia. J. Biol. Chem. 276: 43909–43914, 2001. ; and

[21284] Vidal, R.; Revesz, T.; Rostagno, A.; Kim, E.; Holton, J. L.; Bek, T.; Bojsen-Moller, M.; Braendgaard, H.; Plant, G.; Ghiso, J.; Frangione, B. : A decamer duplication in the 3-prime regi.

[21285] Further studies establishing the function and utilities of ITM2B are found in John Hopkins OMIM database record ID 603904, and in cited publications numbered 8197–8198, 1235 and 12685 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Polymeric Immunoglobulin Receptor (PIGR,

Accession XM\_052013) is another VGAM458 host target gene. PIGR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIGR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIGR BINDING SITE, designated SEQ ID:35935, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21286] Another function of VGAM458 is therefore inhibition of Polymeric Immunoglobulin Receptor (PIGR, Accession XM\_052013). Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIGR. Rhesus Blood Group, D Antigen (RHD, Accession NM\_016124) is another VGAM458 host target gene. RHD BINDING SITE1 and RHD BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RHD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RHD BINDING SITE1 and RHD BINDING SITE2, designated SEQ ID:18214 and SEQ ID:18334 respectively, to the nu-

cleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21287] Another function of VGAM458 is therefore inhibition of Rhesus Blood Group, D Antigen (RHD, Accession NM\_016124), a gene which Major antigen of the RH system. Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RHD. The function of RHD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74.DKFZP434C1715 (Accession XM\_098421) is another VGAM458 host target gene. DKFZP434C1715 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434C1715, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434C1715 BINDING SITE, designated SEQ ID:41675, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21288] Another function of VGAM458 is therefore inhibition of DKFZP434C1715 (Accession XM\_098421). Accordingly,

utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434C1715. GFR (Accession NM\_012294) is another VGAM458 host target gene. GFR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GFR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GFR BINDING SITE, designated SEQ ID:14639, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21289] Another function of VGAM458 is therefore inhibition of GFR (Accession NM\_012294). Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GFR. Solute Carrier Family 7, (cationic amino acid transporter,  $\gamma^+$  system) Member 11 (SLC7A11, Accession NM\_014331) is another VGAM458 host target gene. SLC7A11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC7A11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-



trates the complementarity of the nucleotide sequences of SLC7A11 BINDING SITE, designated SEQ ID:15645, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21290] Another function of VGAM458 is therefore inhibition of Solute Carrier Family 7, (cationic amino acid transporter,  $\gamma^+$  system) Member 11 (SLC7A11, Accession NM\_014331). Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC7A11. Ubiquitin Specific Protease 24 (USP24, Accession XM\_165973) is another VGAM458 host target gene. USP24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by USP24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USP24 BINDING SITE, designated SEQ ID:43819, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21291] Another function of VGAM458 is therefore inhibition of Ubiquitin Specific Protease 24 (USP24, Accession XM\_165973). Accordingly, utilities of VGAM458 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with USP24. LOC205251 (Accession XM\_119554) is another VGAM458 host target gene. LOC205251 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC205251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC205251 BINDING SITE, designated SEQ ID:43590, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21292] Another function of VGAM458 is therefore inhibition of LOC205251 (Accession XM\_119554). Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC205251. LOC254251 (Accession XM\_171088) is another VGAM458 host target gene. LOC254251 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC254251 BINDING SITE, designated SEQ ID:45899, to the nucleotide sequence of VGAM458 RNA, herein designated VGAM RNA, also designated SEQ ID:3169.

[21293] Another function of VGAM458 is therefore inhibition of LOC254251 (Accession XM\_171088). Accordingly, utilities of VGAM458 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254251. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 459 (VGAM459) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21294] VGAM459 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM459 was detected is described hereinabove with reference to Figs. 1–8.

[21295] VGAM459 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ectromelia Virus. VGAM459 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21296] VGAM459 gene encodes a VGAM459 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM459 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM459 precursor RNA is designated SEQ ID:445, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:445 is located at position 78528 relative to the genome of Ectromelia Virus.

[21297] VGAM459 precursor RNA folds onto itself, forming VGAM459 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21298] An enzyme complex designated DICER COMPLEX, `dices` the VGAM459 folded precursor RNA into VGAM459 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM459 RNA is designated SEQ ID:3170, and is provided hereinbelow with reference to the sequence listing part.

[21299] VGAM459 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM459 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM459 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21300] VGAM459 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM459 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM459 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM459 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM459 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21301] The complementary binding of VGAM459 RNA, herein designated VGAM RNA, to host target binding sites on VGAM459 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM459 host target RNA into VGAM459 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21302] It is appreciated that VGAM459 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM459 host target genes. The mRNA of each one of this plurality of VGAM459 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM459 RNA, herein designated VGAM RNA, and which when bound by VGAM459 RNA causes inhibition of translation of respective one or more VGAM459 host target proteins.

[21303] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM459 gene, herein designated VGAM GENE, on one or more VGAM459 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[21304] It is yet further appreciated that a function of VGAM459 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of viral infection by Ectromelia Virus. Specific functions, and accordingly utilities, of VGAM459 correlate with, and may be deduced from, the identity of the host target genes which VGAM459 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21305] Nucleotide sequences of the VGAM459 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM459 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM459 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM459 are further described hereinbelow with reference to Table 1.

[21306] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM459 host target RNA, and schematic



representation of the complementarity of each of these host target binding sites to VGAM459 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21307] As mentioned hereinabove with reference to Fig. 1, a function of VGAM459 gene, herein designated VGAM is inhibition of expression of VGAM459 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM459 correlate with, and may be deduced from, the identity of the target genes which VGAM459 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21308] Cadherin, EGF LAG Seven-pass G-type Receptor 1 (flamingo homolog, Drosophila) (CELSR1, Accession NM\_014246) is a VGAM459 host target gene. CELSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CELSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CELSR1 BINDING SITE, designated SEQ ID:15519, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21309] A function of VGAM459 is therefore inhibition of Cadherin, EGF LAG Seven-pass G-type Receptor 1 (flamingo homolog, *Drosophila*) (CELSR1, Accession NM\_014246), a gene which is involved in contact-mediated communication. Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CELSR1. The function of CELSR1 has been established by previous studies. By screening a mouse embryonic cDNA library, Hadjantonakis et al. (1997, 1998) obtained a cDNA encoding a 3,034-amino acid 7-pass transmembrane G protein-coupled receptor, which they termed cadherin EGF LAG seven-pass G-type receptor-1 (OMIM Ref. No. Celsr1). Celsr1 contains motifs that are recognized as mediators of protein-protein interactions. In its extracellular region it has a block of contiguous cadherin repeats in the N terminus and then a region with 7 epidermal growth factor (EGF; 131530)-like repeats interrupted by 2 laminin A (OMIM Ref. No. 150320) G-type (LAG) repeats. By in situ hybridization and RT-PCR analysis, Hadjantonakis et al. (1997) detected significant levels of Celsr1 in neural tube, brain, lung epithelium, and nascent eyelid in day 11.5 mouse embryos. In adult mice, expression was detected in spinal cord, eye,

and brain, chiefly in ependymal cells lining the lateral, third, and fourth ventricles. The structure, putative G-linked signaling properties, and restricted expression of the Celsr1 protein suggest that it is a receptor involved in contact-mediated communication.

[21310] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21311] Hadjantonakis, A.-K.; Formstone, C. J.; Little, P. F. R. : mCelsr1 is an evolutionarily conserved seven-pass trans-membrane receptor and is expressed during mouse embryonic development. Mech. Dev. 78: 91-95, 1998. ; and

[21312] Hadjantonakis, A.-K.; Sheward, W. J.; Harmar, A. J.; de Galan, L.; Hoovers, J. M. N.; Little, P. F. R. : Celsr1, a neural-specific gene encoding an unusual seven-pass trans-membrane rece.

[21313] Further studies establishing the function and utilities of CELSR1 are found in John Hopkins OMIM database record ID 604523, and in cited publications numbered 6933-693 and 7438 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neurobeachin (NBEA, Accession XM\_170732) is another VGAM459 host target gene. NBEA BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NBEA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NBEA BINDING SITE, designated SEQ ID:45490, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21314] Another function of VGAM459 is therefore inhibition of Neurobeachin (NBEA, Accession XM\_170732), a gene which may mediate protein-protein interactions. Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NBEA. The function of NBEA has been established by previous studies. The targeting of protein kinase A (PKA) actions to specific subcellular sites is mediated in part by A-kinase anchor proteins (AKAPs; OMIM Ref. No. 602449), a large and diverse group of proteins that includes neurobeachin. AKAPs reside at distinct subcellular locations and possess high-affinity binding sites for the type II regulatory subunit isoforms of PKA. By immunoscreening a chicken brain cDNA expression library with antibody to synaptic plasma membranes, followed by

probing of a mouse cDNA library, Wang et al. (2000) identified a predominantly brain-expressed cDNA encoding Nbea. Sequence analysis predicted that the 2,936-amino acid cytosolic protein contains a series of C-terminal WD40 repeats preceded by an approximately 280-amino acid BEACH (for beige and Chediak-Higashi) domain, originally identified by Nagle et al. (1996) in LYST (OMIM Ref. No. 606897), the protein mutated in the Chediak-Higashi syndrome. BEACH is a conserved sequence, larger than a protein-protein interaction site, that is also found in human FAN (NSMAF; 603043) and the partial sequence known as BGL or CDC4L. Binding analysis showed that region B of Nbea binds with high affinity and specificity to the type II regulatory subunits, preferentially RII- $\alpha$ , of PKA. Helical wheel analysis revealed the potential for an amphiphilic  $\alpha$  helix and the formation of a core binding site. Northern blot analysis of chicken tissue and Western blot analysis of mouse tissue indicated that Nbea expression is selective for brain. Immunocytochemical analysis demonstrated association with pleomorphic tubulovesicular endomembranes near the trans sides of Golgi stacks and in a subpopulation of synapses. Immunofluorescence microscopy revealed that Nbea associ-

ation with Golgi–near membranes is stimulated by GTP–gamma–S and dispersed by brefeldin A.

[21315] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21316] Gilbert, D. J.; Engel, H.; Wang, X.; Grzeschik, K.–H.; Copeland, N. G.; Jenkins, N. A.; Kilimann, M. W. : The neurobeachin gene (Nbea) identifies a new region of homology between mouse central chromosome 3 and human chromosome 13q13. *Mamm. Genome* 10: 1030–1031, 1999. ; and

[21317] Nagle, D. L.; Karim, M. A.; Woolf, E. A.; Holmgren, L.; Bork, P.; Misumi, D. J.; McGrail, S. H.; Dussault, B. J., Jr.; Perou, C. M.; Boissy, R. E.; Duyk, G. M.; Spritz, R. A.; Moore, K.

[21318] Further studies establishing the function and utilities of NBEA are found in John Hopkins OMIM database record ID 604889, and in cited publications numbered 6950–6952 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Sodium Channel, Voltage–gated, Type III, Alpha Polypeptide (SCN3A, Accession NM\_006922) is another VGAM459 host target gene. SCN3A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by

SCN3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCN3A BINDING SITE, designated SEQ ID:13797, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21319] Another function of VGAM459 is therefore inhibition of Sodium Channel, Voltage-gated, Type III, Alpha Polypeptide (SCN3A, Accession NM\_006922), a gene which may be important for maintaining neural membrane excitability. Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCN3A. The function of SCN3A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM124. Ubiquitin-like 3 (UBL3, Accession NM\_007106) is another VGAM459 host target gene. UBL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of UBL3 BINDING SITE, designated SEQ ID:13963, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21320] Another function of VGAM459 is therefore inhibition of Ubiquitin-like 3 (UBL3, Accession NM\_007106), a gene which appears to have a diverse range of cellular functions. Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBL3. The function of UBL3 has been established by previous studies. Ubiquitin (OMIM Ref. No. 191320) targets proteins for degradation by the 26S proteasome (see OMIM Ref. No. 603146). In contrast, ubiquitin-like (UBL) proteins (e.g., UBL1; 601912) may not be directly involved in protein degradation, but appear to have a diverse range of cellular functions (reviewed by Hodges et al., 1998). Chadwick et al. (1999) identified the *Drosophila* UBL3 gene. By searching an EST database using a *Drosophila* UBL3 cDNA as the query, they identified a human UBL3 EST. Using the EST, they isolated human keratinocyte stem cell cDNAs representing the complete UBL3 coding sequence. The deduced 117-amino acid human UBL3 protein contains 2 potential N-glycosylation



sites, a potential protein kinase C phosphorylation site, and a potential C-terminal prenylation site. It is relatively hydrophilic with no predicted transmembrane domains. Human UBL3 shares 69% amino acid sequence identity with 1 form of *Drosophila* UBL3 and 99% identity with mouse Ubl3, a cDNA of which Chadwick et al. (1999) also isolated. Northern blot analysis of human tissues detected 3.5- and 4.5-kb UBL3 transcripts in all tissues tested, namely spleen, thymus, peripheral blood leukocytes, testis, ovary, placenta, prostate, liver, pancreas, small intestine, colon, kidney, heart, lung, brain, and skeletal muscle. Additional transcripts of 2.0 and 3.0 kb were found in testis. Chadwick et al. (1999) identified 3 polyadenylation signals that result in alternatively polyadenylated UBL3 transcripts. By somatic cell hybrid mapping, Chadwick et al. (1999) mapped the human UBL3 gene to chromosome 13. They localized the UBL3 gene to 13q12-q13 using radiation hybrid mapping. Using FISH, Chadwick et al. (1999) mapped the mouse Ubl3 gene to the telomeric end of chromosome 5 in band G2-3, a region showing homology of synteny with human 13q.

[21321] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [21322] Chadwick, B. P.; Kidd, T.; Sgouros, J.; Ish-Horowicz, D.; Frischauf, A.-M. : Cloning, mapping and expression of UBL3, a novel ubiquitin-like gene. *Gene* 233: 189-195, 1999. ; and
- [21323] Hodges, M.; Tissot, C.; Freemont, P. S. : : Protein regulation: tag wrestling with relatives of ubiquitin. *Curr. Biol.* 8: R749-R752, 1998.
- [21324] Further studies establishing the function and utilities of UBL3 are found in John Hopkins OMIM database record ID 604711, and in cited publications numbered 4933-4934 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Wilms Tumor 1 (WT1, Accession NM\_024424) is another VGAM459 host target gene. WT1 BINDING SITE1 through WT1 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by WT1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WT1 BINDING SITE1 through WT1 BINDING SITE4, designated SEQ ID:23668, SEQ ID:23672, SEQ ID:23676 and SEQ ID:5952 respectively, to the nucleotide sequence of VGAM459

RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21325] Another function of VGAM459 is therefore inhibition of Wilms Tumor 1 (WT1, Accession NM\_024424). Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WT1. C1q and Tumor Necrosis Factor Related Protein 7 (C1QTNF7, Accession NM\_031911) is another VGAM459 host target gene. C1QTNF7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1QTNF7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1QTNF7 BINDING SITE, designated SEQ ID:25663, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21326] Another function of VGAM459 is therefore inhibition of C1q and Tumor Necrosis Factor Related Protein 7 (C1QTNF7, Accession NM\_031911). Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1QTNF7. HELO1 (Accession NM\_021814) is another

VGAM459 host target gene. HELO1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HELO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HELO1 BINDING SITE, designated SEQ ID:22385, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21327] Another function of VGAM459 is therefore inhibition of HELO1 (Accession NM\_021814). Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HELO1. KIAA1203 (Accession XM\_049683) is another VGAM459 host target gene. KIAA1203 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1203, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1203 BINDING SITE, designated SEQ ID:35466, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21328] Another function of VGAM459 is therefore inhibition of KIAA1203 (Accession XM\_049683). Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1203. MGC14161 (Accession NM\_032892) is another VGAM459 host target gene. MGC14161 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC14161, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC14161 BINDING SITE, designated SEQ ID:26715, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21329] Another function of VGAM459 is therefore inhibition of MGC14161 (Accession NM\_032892). Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC14161. PANK (Accession NM\_138316) is another VGAM459 host target gene. PANK BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PANK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PANK BINDING SITE, designated SEQ ID:28717, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21330] Another function of VGAM459 is therefore inhibition of PANK (Accession NM\_138316). Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PANK. LOC133686 (Accession XM\_059667) is another VGAM459 host target gene. LOC133686 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133686, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133686 BINDING SITE, designated SEQ ID:37058, to the nucleotide sequence of VGAM459 RNA, herein designated VGAM RNA, also designated SEQ ID:3170.

[21331] Another function of VGAM459 is therefore inhibition of LOC133686 (Accession XM\_059667). Accordingly, utilities of VGAM459 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC133686. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 460 (VGAM460) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21332] VGAM460 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM460 was detected is described hereinabove with reference to Figs. 1–8.

[21333] VGAM460 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM460 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21334] VGAM460 gene encodes a VGAM460 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM460 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM460 precursor RNA is designated SEQ ID:446, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:446 is

located at position 69643 relative to the genome of Vari-  
ola Virus.

[21335] VGAM460 precursor RNA folds onto itself, forming VGAM460 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21336] An enzyme complex designated DICER COMPLEX, `dices` the VGAM460 folded precursor RNA into VGAM460 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM460 RNA is designated SEQ ID:3171, and is provided hereinbelow with reference to the sequence listing part.

[21337] VGAM460 host target gene, herein designated VGAM



HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM460 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM460 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[21338] VGAM460 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM460 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM460 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM460 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM460 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[21339] The complementary binding of VGAM460 RNA, herein designated VGAM RNA, to host target binding sites on VGAM460 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM460 host target RNA into VGAM460 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21340] It is appreciated that VGAM460 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM460 host target genes. The mRNA of each one of this plurality of VGAM460 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM460 RNA, herein designated VGAM RNA, and which when bound by VGAM460 RNA causes inhibition of translation of respective one or more VGAM460

host target proteins.

[21341] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM460 gene, herein designated VGAM GENE, on one or more VGAM460 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21342] It is yet further appreciated that a function of VGAM460 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of viral infection by Variola Virus. Specific func-

tions, and accordingly utilities, of VGAM460 correlate with, and may be deduced from, the identity of the host target genes which VGAM460 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [21343] Nucleotide sequences of the VGAM460 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM460 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM460 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM460 are further described hereinbelow with reference to Table 1.
- [21344] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM460 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM460 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21345] As mentioned hereinabove with reference to Fig. 1, a function of VGAM460 gene, herein designated VGAM is inhibition of expression of VGAM460 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM460 correlate with, and may be deduced from, the identity of the target genes which VGAM460 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21346] 2',3'-cyclic Nucleotide 3' Phosphodiesterase (CNP, Accession NM\_033133) is a VGAM460 host target gene. CNP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNP BINDING SITE, designated SEQ ID:26976, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21347] A function of VGAM460 is therefore inhibition of 2',3'-cyclic Nucleotide 3' Phosphodiesterase (CNP, Accession NM\_033133), a gene which can link tubulin to membranes and may regulate cytoplasmic microtubule distribution. Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNP. The function of CNP and its association with various diseases and clinical conditions, has been established by previous studies, as described

hereinabove with reference to VGAM443. Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437) is another VGAM460 host target gene. NCOA4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCOA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA4 BINDING SITE, designated SEQ ID:11922, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21348] Another function of VGAM460 is therefore inhibition of Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437), a gene which Binds and activates androgen receptor (AR) in ligand-dependent manner. Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA4. The function of NCOA4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM420. Transcription Factor Binding to IGHM Enhancer 3 (TFE3, Accession NM\_006521) is another VGAM460 host target gene. TFE3 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TFE3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TFE3 BINDING SITE, designated SEQ ID:13274, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21349] Another function of VGAM460 is therefore inhibition of Transcription Factor Binding to IGHM Enhancer 3 (TFE3, Accession NM\_006521), a gene which is a positive-acting transcription factor that binds to the immunoglobulin enhancer *mu*3 motif. Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TFE3. The function of TFE3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM443. Vacuolar Protein Sorting 26 (yeast) (VPS26, Accession NM\_004896) is another VGAM460 host target gene. VPS26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VPS26, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VPS26 BINDING SITE, designated SEQ ID:11329, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21350] Another function of VGAM460 is therefore inhibition of Vacuolar Protein Sorting 26 (yeast) (VPS26, Accession NM\_004896), a gene which is a sorting protein– ensures the proper delivery of organelle–specific proteins. Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VPS26. The function of VPS26 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM315. Caspase Recruitment Domain Family, Member 6 (CARD6, Accession NM\_032587) is another VGAM460 host target gene. CARD6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CARD6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide



sequences of CARD6 BINDING SITE, designated SEQ ID:26322, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21351] Another function of VGAM460 is therefore inhibition of Caspase Recruitment Domain Family, Member 6 (CARD6, Accession NM\_032587). Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CARD6. DKFZp761K1423 (Accession NM\_018422) is another VGAM460 host target gene. DKFZp761K1423 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp761K1423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761K1423 BINDING SITE, designated SEQ ID:20475, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21352] Another function of VGAM460 is therefore inhibition of DKFZp761K1423 (Accession NM\_018422). Accordingly, utilities of VGAM460 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with DKFZp761K1423. KIAA0090 (Accession XM\_114045) is another VGAM460 host target gene. KIAA0090 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0090, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0090 BINDING SITE, designated SEQ ID:42655, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21353] Another function of VGAM460 is therefore inhibition of KIAA0090 (Accession XM\_114045). Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0090. KIAA0543 (Accession XM\_044213) is another VGAM460 host target gene. KIAA0543 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0543, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0543 BINDING SITE, designated SEQ ID:34180, to the

nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21354] Another function of VGAM460 is therefore inhibition of KIAA0543 (Accession XM\_044213). Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0543. Lymphocyte Antigen 75 (LY75, Accession NM\_002349) is another VGAM460 host target gene. LY75 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LY75, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LY75 BINDING SITE, designated SEQ ID:8152, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21355] Another function of VGAM460 is therefore inhibition of Lymphocyte Antigen 75 (LY75, Accession NM\_002349). Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LY75. LOC146179 (Accession XM\_085354) is another VGAM460 host target gene. LOC146179 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC146179, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146179 BINDING SITE, designated SEQ ID:38077, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21356] Another function of VGAM460 is therefore inhibition of LOC146179 (Accession XM\_085354). Accordingly, utilities of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146179. LOC221399 (Accession XM\_168134) is another VGAM460 host target gene. LOC221399 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221399, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221399 BINDING SITE, designated SEQ ID:45053, to the nucleotide sequence of VGAM460 RNA, herein designated VGAM RNA, also designated SEQ ID:3171.

[21357] Another function of VGAM460 is therefore inhibition of LOC221399 (Accession XM\_168134). Accordingly, utilities

of VGAM460 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221399. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 461 (VGAM461) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21358] VGAM461 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM461 was detected is described hereinabove with reference to Figs. 1–8.

[21359] VGAM461 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM461 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21360] VGAM461 gene encodes a VGAM461 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM461 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM461 precursor RNA is designated SEQ

ID:447, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:447 is located at position 119548 relative to the genome of Variola Virus.

[21361] VGAM461 precursor RNA folds onto itself, forming VGAM461 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21362] An enzyme complex designated DICER COMPLEX, `dices` the VGAM461 folded precursor RNA into VGAM461 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM461 RNA is designated SEQ ID:3172, and is provided hereinbelow with reference to the sequence

listing part.

[21363] VGAM461 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM461 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM461 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21364] VGAM461 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM461 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM461 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM461 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM461 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21365] The complementary binding of VGAM461 RNA, herein designated VGAM RNA, to host target binding sites on VGAM461 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM461 host target RNA into VGAM461 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21366] It is appreciated that VGAM461 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM461 host target genes. The mRNA of each one of this plurality of VGAM461 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM461 RNA, herein designated VGAM



RNA, and which when bound by VGAM461 RNA causes inhibition of translation of respective one or more VGAM461 host target proteins.

[21367] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM461 gene, herein designated VGAM GENE, on one or more VGAM461 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21368] It is yet further appreciated that a function of VGAM461 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM461 include diagnosis, prevention and treatment of viral infection by Variola Virus. Specific functions, and accordingly utilities, of VGAM461 correlate with, and may be deduced from, the identity of the host target genes which VGAM461 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21369] Nucleotide sequences of the VGAM461 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM461 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM461 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM461 are further described hereinbelow with reference to Table 1.

[21370] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM461 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM461 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21371] As mentioned hereinabove with reference to Fig. 1, a function of VGAM461 gene, herein designated VGAM is

inhibition of expression of VGAM461 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM461 correlate with, and may be deduced from, the identity of the target genes which VGAM461 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21372] FLJ14009 (Accession NM\_024760) is a VGAM461 host target gene. FLJ14009 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ14009, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14009 BINDING SITE, designated SEQ ID:24112, to the nucleotide sequence of VGAM461 RNA, herein designated VGAM RNA, also designated SEQ ID:3172.

[21373] A function of VGAM461 is therefore inhibition of FLJ14009 (Accession NM\_024760). Accordingly, utilities of VGAM461 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14009. KIAA0332 (Accession XM\_031553) is another VGAM461 host target gene. KIAA0332 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by KIAA0332, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0332 BINDING SITE, designated SEQ ID:31416, to the nucleotide sequence of VGAM461 RNA, herein designated VGAM RNA, also designated SEQ ID:3172.

[21374] Another function of VGAM461 is therefore inhibition of KIAA0332 (Accession XM\_031553). Accordingly, utilities of VGAM461 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0332. PRO1768 (Accession NM\_014099) is another VGAM461 host target gene. PRO1768 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRO1768, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1768 BINDING SITE, designated SEQ ID:15323, to the nucleotide sequence of VGAM461 RNA, herein designated VGAM RNA, also designated SEQ ID:3172.

[21375] Another function of VGAM461 is therefore inhibition of PRO1768 (Accession NM\_014099). Accordingly, utilities of

VGAM461 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1768. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 462 (VGAM462) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21376] VGAM462 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM462 was detected is described hereinabove with reference to Figs. 1–8.

[21377] VGAM462 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM462 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21378] VGAM462 gene encodes a VGAM462 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM462 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM462 precursor RNA is designated SEQ ID:448, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:448 is located at position 168878 relative to the genome of Vari-  
ola Virus.

[21379] VGAM462 precursor RNA folds onto itself, forming VGAM462 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21380] An enzyme complex designated DICER COMPLEX, `dices` the VGAM462 folded precursor RNA into VGAM462 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM462 RNA is designated SEQ ID:3173, and is provided hereinbelow with reference to the sequence listing part.

[21381] VGAM462 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM462 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM462 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21382] VGAM462 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM462 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM462 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM462 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM462 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21383] The complementary binding of VGAM462 RNA, herein designated VGAM RNA, to host target binding sites on VGAM462 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM462 host target RNA into VGAM462 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21384] It is appreciated that VGAM462 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM462 host target genes. The mRNA of each one of this plurality of VGAM462 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM462 RNA, herein designated VGAM RNA, and which when bound by VGAM462 RNA causes in-



hibition of translation of respective one or more VGAM462 host target proteins.

[21385] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM462 gene, herein designated VGAM GENE, on one or more VGAM462 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21386] It is yet further appreciated that a function of VGAM462 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM462 include diagnosis, prevention and

treatment of viral infection by Variola Virus. Specific functions, and accordingly utilities, of VGAM462 correlate with, and may be deduced from, the identity of the host target genes which VGAM462 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [21387] Nucleotide sequences of the VGAM462 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM462 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM462 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM462 are further described hereinbelow with reference to Table 1.
- [21388] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM462 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM462 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21389] As mentioned hereinabove with reference to Fig. 1, a function of VGAM462 gene, herein designated VGAM is inhibition of expression of VGAM462 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM462 correlate with, and may be deduced from, the identity of the target genes which VGAM462 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21390] 5-hydroxytryptamine (serotonin) Receptor 6 (HTR6, Accession NM\_000871) is a VGAM462 host target gene. HTR6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HTR6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HTR6 BINDING SITE, designated SEQ ID:6548, to the nucleotide sequence of VGAM462 RNA, herein designated VGAM RNA, also designated SEQ ID:3173.

[21391] A function of VGAM462 is therefore inhibition of 5-hydroxytryptamine (serotonin) Receptor 6 (HTR6, Accession NM\_000871), a gene which stimulates adenylate cyclase. Accordingly, utilities of VGAM462 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTR6. The function of HTR6 and its association with various diseases and clinical conditions, has been established by previous studies, as de-

scribed hereinabove with reference to VGAM326. Cat Eye Syndrome Chromosome Region, Candidate 7 (CECR7, Accession XM\_086803) is another VGAM462 host target gene. CECR7 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CECR7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CECR7 BINDING SITE, designated SEQ ID:38876, to the nucleotide sequence of VGAM462 RNA, herein designated VGAM RNA, also designated SEQ ID:3173.

[21392] Another function of VGAM462 is therefore inhibition of Cat Eye Syndrome Chromosome Region, Candidate 7 (CECR7, Accession XM\_086803). Accordingly, utilities of VGAM462 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CECR7. KIAA1203 (Accession XM\_049683) is another VGAM462 host target gene. KIAA1203 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1203, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA1203 BINDING SITE, designated SEQ ID:35467, to the nucleotide sequence of VGAM462 RNA, herein designated VGAM RNA, also designated SEQ ID:3173.

[21393] Another function of VGAM462 is therefore inhibition of KIAA1203 (Accession XM\_049683). Accordingly, utilities of VGAM462 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1203. KIAA1535 (Accession XM\_086565) is another VGAM462 host target gene. KIAA1535 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1535, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1535 BINDING SITE, designated SEQ ID:38763, to the nucleotide sequence of VGAM462 RNA, herein designated VGAM RNA, also designated SEQ ID:3173.

[21394] Another function of VGAM462 is therefore inhibition of KIAA1535 (Accession XM\_086565). Accordingly, utilities of VGAM462 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1535. KIAA1894 (Accession XM\_058025) is another

VGAM462 host target gene. KIAA1894 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1894 BINDING SITE, designated SEQ ID:36560, to the nucleotide sequence of VGAM462 RNA, herein designated VGAM RNA, also designated SEQ ID:3173.

[21395] Another function of VGAM462 is therefore inhibition of KIAA1894 (Accession XM\_058025). Accordingly, utilities of VGAM462 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1894. LOC151171 (Accession XM\_087116) is another VGAM462 host target gene. LOC151171 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151171, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151171 BINDING SITE, designated SEQ ID:39065, to the nucleotide sequence of VGAM462 RNA, herein designated VGAM RNA, also designated SEQ ID:3173.

[21396] Another function of VGAM462 is therefore inhibition of LOC151171 (Accession XM\_087116). Accordingly, utilities of VGAM462 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151171. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 463 (VGAM463) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21397] VGAM463 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM463 was detected is described hereinabove with reference to Figs. 1–8.

[21398] VGAM463 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM463 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21399] VGAM463 gene encodes a VGAM463 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM463 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM463 precursor RNA is designated SEQ ID:449, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:449 is located at position 169316 relative to the genome of Variola Virus.

[21400] VGAM463 precursor RNA folds onto itself, forming VGAM463 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21401] An enzyme complex designated DICER COMPLEX, `dices` the VGAM463 folded precursor RNA into VGAM463 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide se-



quence of VGAM463 RNA is designated SEQ ID:3174, and is provided hereinbelow with reference to the sequence listing part.

[21402] VGAM463 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM463 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM463 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[21403] VGAM463 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM463 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM463 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM463 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM463 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[21404] The complementary binding of VGAM463 RNA, herein designated VGAM RNA, to host target binding sites on VGAM463 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM463 host target RNA into VGAM463 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21405] It is appreciated that VGAM463 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM463 host target genes. The mRNA of each one of this plurality of VGAM463 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM463 RNA, herein designated VGAM RNA, and which when bound by VGAM463 RNA causes inhibition of translation of respective one or more VGAM463 host target proteins.

[21406] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM463 gene, herein designated VGAM GENE, on one or more VGAM463 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21407] It is yet further appreciated that a function of VGAM463 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM463 include diagnosis, prevention and treatment of viral infection by Variola Virus. Specific functions, and accordingly utilities, of VGAM463 correlate with, and may be deduced from, the identity of the host target genes which VGAM463 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21408] Nucleotide sequences of the VGAM463 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM463 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM463 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM463 are further described hereinbelow with reference to Table 1.

[21409] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM463 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM463 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21410] As mentioned hereinabove with reference to Fig. 1, a function of VGAM463 gene, herein designated VGAM is inhibition of expression of VGAM463 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM463 correlate with, and may be deduced from, the identity of the target genes which VGAM463 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21411] Exonuclease 1 (EXO1, Accession NM\_003686) is a VGAM463 host target gene. EXO1 BINDING SITE1 through EXO1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by EXO1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EXO1 BINDING SITE1 through EXO1 BINDING SITE3, designated SEQ ID:9797, SEQ ID:12644 and SEQ ID:28183 respectively, to the nucleotide sequence of VGAM463 RNA, herein designated VGAM RNA, also designated SEQ ID:3174.

[21412] A function of VGAM463 is therefore inhibition of Exonuclease 1 (EXO1, Accession NM\_003686), a gene which excise and replace mismatched segments. Accordingly, utili-

ties of VGAM463 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EXO1. The function of EXO1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM399. KIAA0237 (Accession NM\_014747) is another VGAM463 host target gene. KIAA0237 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0237 BINDING SITE, designated SEQ ID:16447, to the nucleotide sequence of VGAM463 RNA, herein designated VGAM RNA, also designated SEQ ID:3174.

[21413] Another function of VGAM463 is therefore inhibition of KIAA0237 (Accession NM\_014747). Accordingly, utilities of VGAM463 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0237. KIAA0863 (Accession XM\_170863) is another VGAM463 host target gene. KIAA0863 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0863, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0863 BINDING SITE, designated SEQ ID:45634, to the nucleotide sequence of VGAM463 RNA, herein designated VGAM RNA, also designated SEQ ID:3174.

[21414] Another function of VGAM463 is therefore inhibition of KIAA0863 (Accession XM\_170863). Accordingly, utilities of VGAM463 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0863. KIAA1165 (Accession XM\_041162) is another VGAM463 host target gene. KIAA1165 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1165, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1165 BINDING SITE, designated SEQ ID:33474, to the nucleotide sequence of VGAM463 RNA, herein designated VGAM RNA, also designated SEQ ID:3174.

[21415] Another function of VGAM463 is therefore inhibition of KIAA1165 (Accession XM\_041162). Accordingly, utilities of VGAM463 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1165. Purinergic Receptor P2X, Ligand-gated Ion Channel, 5 (P2RX5, Accession NM\_002561) is another VGAM463 host target gene. P2RX5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P2RX5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P2RX5 BINDING SITE, designated SEQ ID:8408, to the nucleotide sequence of VGAM463 RNA, herein designated VGAM RNA, also designated SEQ ID:3174.

[21416] Another function of VGAM463 is therefore inhibition of Purinergic Receptor P2X, Ligand-gated Ion Channel, 5 (P2RX5, Accession NM\_002561). Accordingly, utilities of VGAM463 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P2RX5. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger



464 (VGAM464) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21417] VGAM464 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM464 was detected is described hereinabove with reference to Figs. 1–8.

[21418] VGAM464 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM464 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21419] VGAM464 gene encodes a VGAM464 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM464 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM464 precursor RNA is designated SEQ ID:450, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:450 is located at position 170440 relative to the genome of Variola Virus.

[21420] VGAM464 precursor RNA folds onto itself, forming VGAM464 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[21421] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM464 folded precursor RNA into VGAM464 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 44%) nucleotide se-  
quence of VGAM464 RNA is designated SEQ ID:3175, and  
is provided hereinbelow with reference to the sequence  
listing part.

[21422] VGAM464 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM464 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM464 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21423] VGAM464 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM464 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM464 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM464 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM464 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21424] The complementary binding of VGAM464 RNA, herein designated VGAM RNA, to host target binding sites on VGAM464 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM464 host target RNA into VGAM464 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21425] It is appreciated that VGAM464 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM464 host target genes. The mRNA of each one of this plurality of VGAM464 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM464 RNA, herein designated VGAM RNA, and which when bound by VGAM464 RNA causes inhibition of translation of respective one or more VGAM464 host target proteins.

[21426] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM464 gene, herein designated VGAM GENE, on one or more VGAM464 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21427] It is yet further appreciated that a function of VGAM464 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of viral infection by Variola Virus. Specific functions, and accordingly utilities, of VGAM464 correlate with, and may be deduced from, the identity of the host target genes which VGAM464 binds and inhibits, and the function of these host target genes, as elaborated herein—

below.

- [21428] Nucleotide sequences of the VGAM464 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM464 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM464 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM464 are further described hereinbelow with reference to Table 1.
- [21429] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM464 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM464 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21430] As mentioned hereinabove with reference to Fig. 1, a function of VGAM464 gene, herein designated VGAM is inhibition of expression of VGAM464 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM464 correlate with, and may be deduced from, the identity of the target genes which VGAM464 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21431] Collagen, Type IV, Alpha 4 (COL4A4, Accession NM\_000092) is a VGAM464 host target gene. COL4A4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COL4A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COL4A4 BINDING SITE, designated SEQ ID:5555, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21432] A function of VGAM464 is therefore inhibition of Collagen, Type IV, Alpha 4 (COL4A4, Accession NM\_000092). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COL4A4. Cytochrome P450, 51 (lanosterol 14-alpha-demethylase) (CYP51, Accession NM\_000786) is another VGAM464 host target gene. CYP51 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP51, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP51 BIND-

ING SITE, designated SEQ ID:6438, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21433] Another function of VGAM464 is therefore inhibition of Cytochrome P450, 51 (lanosterol 14- $\alpha$ -demethylase) (CYP51, Accession NM\_000786). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP51.

Development and Differentiation Enhancing Factor 2 (DDEF2, Accession NM\_003887) is another VGAM464 host target gene. DDEF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DDEF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDEF2 BINDING SITE, designated SEQ ID:9968, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21434] Another function of VGAM464 is therefore inhibition of Development and Differentiation Enhancing Factor 2 (DDEF2, Accession NM\_003887), a gene which interacts with members of the Arf and Src family. Accordingly, utili-



ties of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDEF2. The function of DDEF2 has been established by previous studies. By screening human brain cDNAs for those encoding large proteins, Ishikawa et al. (1997) identified a cDNA, which they called KIAA0400, encoding development- and differentiation-enhancing factor-2. They found that the deduced 1,006-amino acid DDEF2 protein contains a 60-amino acid zinc finger motif thought to be associated with GTPase activating protein (GAP) activity. Using PYK2 (OMIM Ref. No. 601212) as bait in a yeast 2-hybrid screen, Andreev et al. (1999) isolated DDEF2, a PYK2-binding protein which they designated PAP. DDEF2 is a multidomain protein composed of an N-terminal alpha-helical region with a coiled-coil motif, followed by a pleckstrin homology domain, an Arf-GAP domain, an ankyrin homology region, a proline-rich region, and a C-terminal SH3 domain. DDEF2 shares 95% sequence identity with the mouse homolog and 68% sequence identity with human DDEF1 (OMIM Ref. No. 605953). Andreev et al. (1999) identified 2 DDEF2 isoforms, designated PAP-alpha and PAP-beta, that differ by deletion of 45 amino acids from the proline-rich region and 172 amino acids

from the N terminus. Northern blot analysis detected expression of an approximately 5.7-kb transcript at high levels in brain, kidney, and heart, and at lower levels in placenta, lung, and pancreas. Immunofluorescence studies demonstrated that DDEF2 is localized in the Golgi apparatus and at the plasma membrane, where it is colocalized with PYK2. DDEF2 forms a stable complex with PYK2 and activation of PYK2 leads to tyrosine phosphorylation of DDEF2 in vivo. The interaction of DDEF2 and PYK2 appears to be mediated by binding of the SH3 domain of DDEF2 to the proline-rich region in the C terminus of PYK2. In addition, in vitro recombinant DDEF2 exhibits strong GAP activity towards the small GTPases ARF1 (OMIM Ref. No. 103180) and ARF5 (OMIM Ref. No. 103188) and weak activity towards ARF6 (OMIM Ref. No. 600464).

[21435] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21436] Andreev, J.; Simon, J.-P.; Sabatini, D. D.; Kam, J.; Plowman, G.; Randazzo, P. A.; Schlessinger, J. : Identification of a new Pyk2 target protein with Arf-GAP activity. *Molec. Cell. Biol.* 19: 2338-2350, 1999. ; and

[21437] Ishikawa, K.; Nagase, T.; Nakajima, D.; Seki, N.; Ohira, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human gene.

[21438] Further studies establishing the function and utilities of DDEF2 are found in John Hopkins OMIM database record ID 603817, and in cited publications numbered 4912 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Huntingtin Interacting Protein 2 (HIP2, Accession NM\_005339) is another VGAM464 host target gene. HIP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HIP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HIP2 BINDING SITE, designated SEQ ID:11815, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21439] Another function of VGAM464 is therefore inhibition of Huntingtin Interacting Protein 2 (HIP2, Accession NM\_005339). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with HIP2. ISL1 Transcription Factor, LIM/homeodomain, (islet-1) (ISL1, Accession NM\_002202) is another VGAM464 host target gene. ISL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ISL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ISL1 BINDING SITE, designated SEQ ID:7960, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21440] Another function of VGAM464 is therefore inhibition of ISL1 Transcription Factor, LIM/homeodomain, (islet-1) (ISL1, Accession NM\_002202), a gene which binds to one of the cis-acting domain of the insulin gene enhancer. Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ISL1. The function of ISL1 has been established by previous studies. Because insulin deficiency, either relative or absolute, is a cardinal feature of noninsulin-dependent diabetes mellitus (NIDDM; 125853), Tanizawa et al. (1994) investigated the possible involvement of mutations in genes that regulate insulin produc-

tion. Rat Isl1 was the first insulin enhancer-binding protein to be isolated; Tanizawa et al. (1994) used the rat gene to isolate a partial human ISL1 cDNA and subsequently to isolate genomic clones. A simple sequence repeat was found in the ISL1 gene. PCR amplification of this region of genomic DNA revealed 12 alleles in St. Louis African-Americans (heterozygosity = 0.87), 14 alleles in black Nigerians (heterozygosity = 0.89), 8 alleles in Japanese (heterozygosity = 0.69), and 8 alleles in Caucasians (heterozygosity = 0.81). Allelic frequencies in the gene did not differ between patients with NIDDM and nondiabetic control subjects in 2 black populations Shimomura et al. (2000) found a nonsense mutation (Q310X) in the ISL1 gene in a Japanese patient with type II diabetes and a strong family history. The mutation led to decreased activity of the islet-1 transcription factor and thus may have been pathogenic. However, as indicated by Fajans et al. (2001), additional genetic and clinical studies were required to determine whether mutations in ISL1 are the cause of another subtype of MODY

[21441] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21442] Shimomura, H.; Sanke, T.; Hanabusa, T.; Tsunoda, K.; Furuta, H.; Nanjo, K. : Nonsense mutation of islet-1 gene (Q310X) found in a type 2 diabetic patient with a strong family history. Diabetes 49: 1597-1600, 2000. ; and

[21443] Tanizawa, Y.; Riggs, A. C.; Dagogo-Jack, S.; Vaxillaire, M.; Froguel, P.; Liu, L.; Donis-Keller, H.; Permutt, M. A. : Isolation of the human LIM/homeodomain gene islet-1 and identificat.

[21444] Further studies establishing the function and utilities of ISL1 are found in John Hopkins OMIM database record ID 600366, and in cited publications numbered 12032 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. O-linked N-acetylglucosamine (GlcNAc) Transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase) (OGT, Accession NM\_003605) is another VGAM464 host target gene. OGT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OGT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OGT BINDING SITE, designated SEQ ID:9661, to the nucleotide sequence of

VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21445] Another function of VGAM464 is therefore inhibition of O-linked N-acetylglucosamine (GlcNAc) Transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase) (OGT, Accession NM\_003605), a gene which has a role in the glycosylation of nuclear and cytoplasmic proteins. Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OGT. The function of OGT has been established by previous studies. O-linked N-acetylglucosamine (O-GlcNAc) transferase (OGT) catalyzes the addition of a single N-acetylglucosamine in O-glycosidic linkage to serine or threonine residues. Since both phosphorylation and glycosylation compete for similar serine or threonine residues, the 2 processes may compete for sites, or they may alter the substrate specificity of nearby sites by steric or electrostatic effects (Lubas et al., 1997). Haltiwanger et al. (1992) purified rat liver OGT and determined that it has a molecular mass of 340 kD. They proposed that OGT exists as a heterotrimeric complex with 2 subunits of 110 kD and 1 of 78 kD. However, using rabbit OGT, Lubas et al. (1997) an-

alyzed the proteolytic fingerprint of both polypeptides and found that the 2 are related. They suggested that the 78 kD band is a proteolytic product of the 110 kD polypeptide or the product of an alternative translation start site. Kreppel et al. (1997) cloned rat cDNAs encoding the 110-kD subunit. Immunofluorescence of human cells expressing rat OGT indicated that OGT is present in both the nucleus and cytosol.

[21446] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21447] Kreppel, L. K.; Blomberg, M. A.; Hart, G. W. : Dynamic glycosylation of nuclear and cytosolic proteins: cloning and characterization of a unique O-GlcNAc transferase with multiple tetratricopeptide repeats. J. Biol. Chem. 272: 9308–9315, 1997. ; and

[21448] Lubas, W. A.; Frank, D. W.; Krause, M.; Hanover, J. A. : O-linked GlcNAc transferase is a conserved nucleocytoplasmic protein containing tetratricopeptide repeats. J. Biol. Chem. 272: 9.

[21449] Further studies establishing the function and utilities of OGT are found in John Hopkins OMIM database record ID 300255, and in cited publications numbered 9074–9078



listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Platelet-activating Factor Acetylhydrolase, Isoform Ib, Alpha Subunit 45kDa (PAFAH1B1, Accession NM\_000430) is another VGAM464 host target gene. PAFAH1B1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAFAH1B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAFAH1B1 BINDING SITE, designated SEQ ID:6012, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21450] Another function of VGAM464 is therefore inhibition of Platelet-activating Factor Acetylhydrolase, Isoform Ib, Alpha Subunit 45kDa (PAFAH1B1, Accession NM\_000430). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAFAH1B1. Plastin 1 (I isoform) (PLS1, Accession NM\_002670) is another VGAM464 host target gene. PLS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLS1, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLS1 BINDING SITE, designated SEQ ID:8541, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21451] Another function of VGAM464 is therefore inhibition of Plastin 1 (I isoform) (PLS1, Accession NM\_002670). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLS1. RAS P21 Protein Activator (GTPase activating protein) 1 (RASA1, Accession NM\_022650) is another VGAM464 host target gene. RASA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RASA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASA1 BINDING SITE, designated SEQ ID:22904, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21452] Another function of VGAM464 is therefore inhibition of RAS P21 Protein Activator (GTPase activating protein) 1 (RASA1, Accession NM\_022650), a gene which is involved

in the control of cellular proliferation and differentiation. Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASA1. The function of RASA1 has been established by previous studies. The RAS gene family encodes membrane-associated, guanine nucleotide-binding proteins (p21) that are involved in the control of cellular proliferation and differentiation. Similar to other guanine-binding proteins (such as the heterotrimeric G proteins), the RAS proteins cycle between an active guanosine-triphosphate (GTP) bound form and an inactive, guanosine-diphosphate (GDP) bound form. The weak intrinsic GTPase activity of RAS proteins is greatly enhanced by the action of GTPase-activating proteins (GAPs). GAP is an effector of RAS oncogene action. See also RASA2 (OMIM Ref. No. 601589). Trahey et al. (1988) purified guanosine triphosphatase-activating protein from placenta and obtained internal amino acid sequence of the protein from which they cloned 2 classes of cDNA. One class predicted a protein with molecular weight similar to purified GAP and corresponded to the human equivalent of bovine GAP cDNA. The other predicted a smaller protein with a different N-terminal sequence, presumably the result of differ-

ential splicing. Both types of cDNAs produced protein with GAP activity. Point mutations in RAS genes ('activating' or oncogenic mutants) decrease the intrinsic GTPase activity of RAS and are insensitive to stimulation by GAPs. This suggested to Friedman et al. (1993) that at least some of the transforming activity of mutant RAS is conferred by the RAS protein being constitutively activated in its GTP-bound state. Mutations in RAS that render it insensitive to GAP regulation result in tumor formation. Mutations in GAP that ablate its ability to downregulate RAS might result in a similar phenotype. To test this hypothesis, Friedman et al. (1993) analyzed 188 human tumor samples for mutations within the catalytic domain of the GAP gene and for mutations within its C-terminal SH2 region. Although no mutations could be demonstrated in the catalytic domain, 3 different nonsense mutations were observed in basal cell carcinomas. The region in which the mutations were clustered is A/T rich, raising the possibility that UV radiation is a contributing factor. The 3 mutations were found in the first 5 tumors examined. No abnormality was found in 16 other basal cell carcinomas. Thus, the apparent prevalence of GAP mutation was about 14% (3 of 21). The tumors analyzed included a great variety, including

cancers of thyroid, lung, breast, colon, and pancreas. No GAP mutation was found in any of these. Mitsudomi et al. (1994) could not demonstrate mutations in the catalytic domain of the GAP gene in human lung cancer cell lines.

[21453] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21454] Friedman, E.; Gejman, P. V.; Martin, G. A.; McCormick, F. : Nonsense mutations in the C-terminal SH2 region of the GTPase activating protein (GAP) gene in human tumours. Nature Genet. 5: 242–247, 1993. ; and

[21455] Trahey, M.; Wong, G.; Halenbeck, R.; Rubinfeld, B.; Martin, G. A.; Ladner, M.; Long, C. M.; Crosier, W. J.; Watt, K.; Kohts, K.; McCormick, F. : Molecular cloning of two types of GAP c.

[21456] Further studies establishing the function and utilities of RASA1 are found in John Hopkins OMIM database record ID 139150, and in cited publications numbered 4738–4743 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Serine (or cysteine) Proteinase Inhibitor, Clade B (ovalbumin), Member 9 (SERPINB9, Accession NM\_004155) is another VGAM464 host target gene. SERPINB9 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SERPINB9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SERPINB9 BINDING SITE, designated SEQ ID:10367, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21457] Another function of VGAM464 is therefore inhibition of Serine (or cysteine) Proteinase Inhibitor, Clade B (ovalbumin), Member 9 (SERPINB9, Accession NM\_004155), a gene which may be a serpin serine protease inhibitor that interacts with granzyme B (GZMB). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SERPINB9. The function of SERPINB9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM60. Soc-2 Suppressor of Clear Homolog (C. elegans) (SHOC2, Accession NM\_007373) is another VGAM464 host target gene. SHOC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

SHOC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SHOC2 BINDING SITE, designated SEQ ID:14307, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21458] Another function of VGAM464 is therefore inhibition of Soc-2 Suppressor of Clear Homolog (*C. elegans*) (SHOC2, Accession NM\_007373), a gene which may be a regulator of the let-60 ras pathway. Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SHOC2. The function of SHOC2 has been established by previous studies. Activation of fibroblast growth factor (FGF) receptors elicits diverse cellular responses, including growth, mitogenesis, migration, and differentiation. Selfors et al. (1998) shed light on the intracellular signaling pathways that mediate these processes by studies in *Caenorhabditis elegans*. In this organism, they screened for genes that suppress the activity of an activated form of the EGL-15 FGF receptor consistent with the functioning of these genes downstream of EGL-15. Two of these genes were

soc1 and soc2, symbolized thus for 'suppressor of clear (Clr)' phenotype; the third was sem5. Selfors et al. (1998) showed that soc2 encodes a protein composed almost entirely of leucine-rich repeats, a domain implicated in protein-protein interactions. They identified a putative human homolog, SHOC2, which is 54% identical to soc2. They showed that SHOC2 mRNA was expressed in all tissues assayed and that the SHOC2 protein is localized to the cytoplasm. Within the leucine-rich repeats of both soc2 and SHOC2 are 2 YXNX motifs that are potential tyrosine-phosphorylated docking sites for the SEM5/GRB2 Src homology 2 domain. However, phosphorylation of these residues was not required for soc2 function in vivo, and SHOC2 was not observed to be tyrosine phosphorylated in response to FGF stimulation. Selfors et al. (1998) concluded that this genetic system identified a conserved gene implicated in mediating FGF receptor signaling in *C. elegans*. Sieburth et al. (1998) identified and characterized the sur8 gene in *C. elegans*, which positively regulates Ras-mediated signal transduction during vulval development. The authors found that reduction of sur8 function suppresses an activated Ras mutation and dramatically enhances phenotypes of mpk-1 MAP kinase and ksr-1



(OMIM Ref. No. 601132) mutations, whereas increase of sur8 dosage enhances an activated Ras mutation. Sur8 appears to act downstream of or in parallel to Ras but upstream of Raf. Sur8 encodes a conserved protein that is composed predominantly of leucine-rich repeats. The sur8 protein interacts directly with Ras but not with the Ras(P34G) mutant protein, suggesting that sur8 may mediate its effects through Ras binding. By use of EST primers and 5-prime RACE, Sieburth et al. (1998) cloned a structural and functional SUR8 homolog in humans that specifically binds K-Ras (OMIM Ref. No. 190070) and N-Ras (OMIM Ref. No. 164790) but not H-Ras (OMIM Ref. No. 190020) in vitro.

[21459] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21460] Selfors, L. M.; Schutzman, J. L.; Borland, C. Z.; Stern, M. J. : Soc-2 encodes a leucine-rich repeat protein implicated in fibroblast growth factor receptor signaling. Proc. Nat. Acad. Sci. 95: 6903-6908, 1998. ; and

[21461] Sieburth, D. S.; Sun, Q.; Han, M. : SUR-8, a conserved Ras-binding protein with leucine-rich repeats, positively regulates Ras-mediated signaling in C. elegans. Cell 94:

119–130, 1998.

[21462] Further studies establishing the function and utilities of SHOC2 are found in John Hopkins OMIM database record ID 602775, and in cited publications numbered 7648–7649 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ10895 (Accession NM\_019084) is another VGAM464 host target gene. FLJ10895 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10895 BINDING SITE, designated SEQ ID:21160, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21463] Another function of VGAM464 is therefore inhibition of FLJ10895 (Accession NM\_019084). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10895. FLJ20038 (Accession NM\_017634) is another VGAM464 host target gene. FLJ20038 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA

encoded by FLJ20038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20038 BINDING SITE, designated SEQ ID:19142, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21464] Another function of VGAM464 is therefore inhibition of FLJ20038 (Accession NM\_017634). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20038. FLJ23560 (Accession NM\_024685) is another VGAM464 host target gene. FLJ23560 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23560, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23560 BINDING SITE, designated SEQ ID:23997, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21465] Another function of VGAM464 is therefore inhibition of FLJ23560 (Accession NM\_024685). Accordingly, utilities of

VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23560. GFR (Accession NM\_012294) is another VGAM464 host target gene. GFR BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GFR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GFR BINDING SITE, designated SEQ ID:14641, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21466] Another function of VGAM464 is therefore inhibition of GFR (Accession NM\_012294). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GFR. KIAA0258 (Accession NM\_014785) is another VGAM464 host target gene. KIAA0258 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0258, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0258 BINDING SITE,

designated SEQ ID:16645, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21467] Another function of VGAM464 is therefore inhibition of KIAA0258 (Accession NM\_014785). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0258. KIAA0982 (Accession NM\_014023) is another VGAM464 host target gene. KIAA0982 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0982, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0982 BINDING SITE, designated SEQ ID:15250, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21468] Another function of VGAM464 is therefore inhibition of KIAA0982 (Accession NM\_014023). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0982. KIAA1077 (Accession XM\_053496) is another VGAM464 host target gene. KIAA1077 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1077, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1077 BINDING SITE, designated SEQ ID:36097, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21469] Another function of VGAM464 is therefore inhibition of KIAA1077 (Accession XM\_053496). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1077. KIAA1962 (Accession XM\_088567) is another VGAM464 host target gene. KIAA1962 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1962, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1962 BINDING SITE, designated SEQ ID:39834, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21470] Another function of VGAM464 is therefore inhibition of

KIAA1962 (Accession XM\_088567). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1962. MGC23980 (Accession NM\_145005) is another VGAM464 host target gene. MGC23980 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC23980, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC23980 BINDING SITE, designated SEQ ID:29605, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21471] Another function of VGAM464 is therefore inhibition of MGC23980 (Accession NM\_145005). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC23980. RALGPS1A (Accession NM\_014636) is another VGAM464 host target gene. RALGPS1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RALGPS1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of RALGPS1A BINDING SITE, designated SEQ ID:16020, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21472] Another function of VGAM464 is therefore inhibition of RALGPS1A (Accession NM\_014636). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RALGPS1A. TSLRP (Accession NM\_012472) is another VGAM464 host target gene. TSLRP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TSLRP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSLRP BINDING SITE, designated SEQ ID:14853, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21473] Another function of VGAM464 is therefore inhibition of TSLRP (Accession NM\_012472). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSLRP. Ubiquitin-activating Enzyme E1C (UBA3 homolog, yeast)



(UBE1C, Accession NM\_003968) is another VGAM464 host target gene. UBE1C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE1C BINDING SITE, designated SEQ ID:10108, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21474] Another function of VGAM464 is therefore inhibition of Ubiquitin-activating Enzyme E1C (UBA3 homolog, yeast) (UBE1C, Accession NM\_003968). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE1C. LOC144453 (Accession XM\_084869) is another VGAM464 host target gene. LOC144453 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144453, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144453 BINDING SITE, designated SEQ ID:37745, to the nucleotide se-

quence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21475] Another function of VGAM464 is therefore inhibition of LOC144453 (Accession XM\_084869). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144453. LOC144571 (Accession XM\_096630) is another VGAM464 host target gene. LOC144571 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144571, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144571 BINDING SITE, designated SEQ ID:40442, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21476] Another function of VGAM464 is therefore inhibition of LOC144571 (Accession XM\_096630). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144571. LOC145547 (Accession XM\_085167) is another VGAM464 host target gene. LOC145547 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC145547, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145547 BINDING SITE, designated SEQ ID:37896, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21477] Another function of VGAM464 is therefore inhibition of LOC145547 (Accession XM\_085167). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145547. LOC145608 (Accession XM\_096818) is another VGAM464 host target gene. LOC145608 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145608, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145608 BINDING SITE, designated SEQ ID:40542, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21478] Another function of VGAM464 is therefore inhibition of LOC145608 (Accession XM\_096818). Accordingly, utilities

of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145608. LOC221692 (Accession XM\_166420) is another VGAM464 host target gene. LOC221692 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221692, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221692 BINDING SITE, designated SEQ ID:44296, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21479] Another function of VGAM464 is therefore inhibition of LOC221692 (Accession XM\_166420). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221692. LOC253443 (Accession XM\_171074) is another VGAM464 host target gene. LOC253443 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC253443, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC253443 BINDING SITE, designated SEQ ID:45884, to the nucleotide sequence of VGAM464 RNA, herein designated VGAM RNA, also designated SEQ ID:3175.

[21480] Another function of VGAM464 is therefore inhibition of LOC253443 (Accession XM\_171074). Accordingly, utilities of VGAM464 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253443. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 465 (VGAM465) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21481] VGAM465 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM465 was detected is described hereinabove with reference to Figs. 1–8.

[21482] VGAM465 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Variola Virus. VGAM465 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21483] VGAM465 gene encodes a VGAM465 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM465 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM465 precursor RNA is designated SEQ ID:451, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:451 is located at position 183993 relative to the genome of Variola Virus.

[21484] VGAM465 precursor RNA folds onto itself, forming VGAM465 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21485] An enzyme complex designated DICER COMPLEX, `dices` the VGAM465 folded precursor RNA into VGAM465 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM465 RNA is designated SEQ ID:3176, and is provided hereinbelow with reference to the sequence listing part.

[21486] VGAM465 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM465 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM465 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[21487] VGAM465 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM465 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM465 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM465 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM465 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21488] The complementary binding of VGAM465 RNA, herein designated VGAM RNA, to host target binding sites on VGAM465 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM465 host target RNA into VGAM465 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21489] It is appreciated that VGAM465 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents



a plurality of VGAM465 host target genes. The mRNA of each one of this plurality of VGAM465 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM465 RNA, herein designated VGAM RNA, and which when bound by VGAM465 RNA causes inhibition of translation of respective one or more VGAM465 host target proteins.

[21490] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM465 gene, herein designated VGAM GENE, on one or more VGAM465 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[21491] It is yet further appreciated that a function of VGAM465 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of viral infection by Variola Virus. Specific functions, and accordingly utilities, of VGAM465 correlate with, and may be deduced from, the identity of the host target genes which VGAM465 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21492] Nucleotide sequences of the VGAM465 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM465 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM465 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM465 are further described hereinbelow with reference to Table 1.

[21493] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM465 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM465 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21494] As mentioned hereinabove with reference to Fig. 1, a function of VGAM465 gene, herein designated VGAM is inhibition of expression of VGAM465 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM465 correlate with, and may be deduced from, the identity of the target genes which VGAM465 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21495] GLI-Kruppel Family Member GLI2 (GLI2, Accession NM\_030379) is a VGAM465 host target gene. GLI2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GLI2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLI2 BINDING SITE, designated SEQ ID:24935, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21496] A function of VGAM465 is therefore inhibition of GLI-Kruppel Family Member GLI2 (GLI2, Accession

NM\_030379), a gene which may promote tax-dependent transcription of T-cell leukemia virus type 1 genes. Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLI2. The function of GLI2 has been established by previous studies. The GLI gene (OMIM Ref. No. 165220) was discovered and so-named by reason of its amplification in gliomas of the brain. Sequencing of GLI cDNA clones showed the presence of 5 tandem zinc fingers connected by histidine-cysteine links, which indicated that the gene belongs to the family of zinc finger genes related to Kruppel (Kr). The Drosophila gene Kr is a member of the gap class of segmentation genes; thoracic and anterior abdominal segments fail to form in Kr mutant embryos. This suggested to Ruppert et al. (1988) that other genes of this class might prove important in normal or disease states. Indeed, other genes important in neoplasia, such as NMYC (OMIM Ref. No. 164840), LMYC (OMIM Ref. No. 164850), HER2 (OMIM Ref. No. 164870), and NRAS (OMIM Ref. No. 164790), have been identified partly by their homology to previously identified oncogenes. Therefore, Ruppert et al. (1988) used a GLI cDNA fragment encoding the zinc finger region to isolate related

human sequences. Six distinct loci were identified in this manner. Partial sequencing revealed that each open reading frame was capable of encoding fingers with H-C links. Most of these sequences were found to be expressed in several adult tissues. Using DNA from human-rodent hybrid panels in hybridization studies with probes representing each of 6 distinct loci (identified as distinct by patterns of RNA expression and species conservation), Ruppert et al. (1988) demonstrated that the 6 loci are located on 5 different chromosomes: GLI2 was concordant with NMYC on chromosome 2; GLI3 with epidermal growth factor receptor (OMIM Ref. No. 131550) on chromosome 7; HKR1 and HKR2 with APOE (OMIM Ref. No. 107741) on chromosome 19; HKR3 with NRAS on chromosome 1; and HKR4 with MYC (OMIM Ref. No. 190080) on chromosome 8. Animal model experiments lend further support to the function of GLI2. Grachtchouk et al. (2000) showed that transgenic mice overexpressing Gli2 in cutaneous keratinocytes develop multiple basal cell carcinomas (BCCs). These results established Gli2 as a potent oncogene in skin and suggested a pivotal role for this transcription factor in the development of human BCC. Furthermore, they found that overexpression of Gli2 in skin results in

the activation of multiple Sonic hedgehog (SHH; 600725) target genes, a feature of human BCCs. They proposed that irrespective of the genetic alteration eliciting uncontrolled SHH signaling in human BCCs, GLI2 has a central role in the genesis of these tumors.

[21497] It is appreciated that the abovementioned animal model for GLI2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21498] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21499] Grachtchouk, M.; Mo, R.; Yu, S.; Zhang, X.; Sasaki, H.; Hui, C.; Dlugosz, A. A. : Basal cell carcinomas in mice overexpressing Gli2 in skin. (Letter) Nature Genet. 24: 216–217, 2000. ; and

[21500] Ruppert, J. M.; Kinzler, K. W.; Wong, A. J.; Bigner, S. H.; Kao, F.-T.; Law, M. L.; Seuanez, H. N.; O'Brien, S. J.; Vogelstein, B. : The GLI-Kruppel family of human genes. Molec. Cell.

[21501] Further studies establishing the function and utilities of GLI2 are found in John Hopkins OMIM database record ID 165230, and in cited publications numbered 46–4 and 45

listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phenylalanine Hydroxylase (PAH, Accession NM\_000277) is another VGAM465 host target gene. PAH BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PAH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAH BINDING SITE, designated SEQ ID:5824, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21502] Another function of VGAM465 is therefore inhibition of Phenylalanine Hydroxylase (PAH, Accession NM\_000277). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAH. XT3 (Accession NM\_020208) is another VGAM465 host target gene. XT3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XT3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XT3 BINDING

SITE, designated SEQ ID:21444, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21503] Another function of VGAM465 is therefore inhibition of XT3 (Accession NM\_020208), a gene which is a Kidney-specific orphan transporter. Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XT3. The function of XT3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM21.DKFZp762M136 (Accession XM\_035635) is another VGAM465 host target gene. DKFZp762M136 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp762M136, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762M136 BINDING SITE, designated SEQ ID:32302, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21504] Another function of VGAM465 is therefore inhibition of



DKFZp762M136 (Accession XM\_035635). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp762M136. FLJ20156 (Accession NM\_017691) is another VGAM465 host target gene. FLJ20156 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20156, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20156 BINDING SITE, designated SEQ ID:19247, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21505] Another function of VGAM465 is therefore inhibition of FLJ20156 (Accession NM\_017691). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20156. FLJ20489 (Accession NM\_017842) is another VGAM465 host target gene. FLJ20489 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20489, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ20489 BINDING SITE, designated SEQ ID:19505, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21506] Another function of VGAM465 is therefore inhibition of FLJ20489 (Accession NM\_017842). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20489. Glutamate Receptor Interacting Protein 1 (GRIP1, Accession XM\_047362) is another VGAM465 host target gene. GRIP1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GRIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRIP1 BINDING SITE, designated SEQ ID:34963, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21507] Another function of VGAM465 is therefore inhibition of Glutamate Receptor Interacting Protein 1 (GRIP1, Accession XM\_047362). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRIP1. HT002

(Accession NM\_014066) is another VGAM465 host target gene. HT002 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HT002, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HT002 BINDING SITE, designated SEQ ID:15279, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21508] Another function of VGAM465 is therefore inhibition of HT002 (Accession NM\_014066). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HT002. KIAA0469 (Accession NM\_014851) is another VGAM465 host target gene. KIAA0469 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0469, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0469 BINDING SITE, designated SEQ ID:16892, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3176.

[21509] Another function of VGAM465 is therefore inhibition of KIAA0469 (Accession NM\_014851). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0469. KIAA1554 (Accession XM\_170834) is another VGAM465 host target gene. KIAA1554 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1554, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1554 BINDING SITE, designated SEQ ID:45615, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21510] Another function of VGAM465 is therefore inhibition of KIAA1554 (Accession XM\_170834). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1554. LOC146272 (Accession XM\_085396) is another VGAM465 host target gene. LOC146272 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146272, corresponding

to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146272 BINDING SITE, designated SEQ ID:38119, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21511] Another function of VGAM465 is therefore inhibition of LOC146272 (Accession XM\_085396). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146272. LOC92078 (Accession XM\_042684) is another VGAM465 host target gene. LOC92078 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92078 BINDING SITE, designated SEQ ID:33747, to the nucleotide sequence of VGAM465 RNA, herein designated VGAM RNA, also designated SEQ ID:3176.

[21512] Another function of VGAM465 is therefore inhibition of LOC92078 (Accession XM\_042684). Accordingly, utilities of VGAM465 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC92078. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 466 (VGAM466) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21513] VGAM466 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM466 was detected is described hereinabove with reference to Figs. 1–8.

[21514] VGAM466 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Autographa Californica Nucleopolyhedrovirus. VGAM466 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21515] VGAM466 gene encodes a VGAM466 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM466 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM466 precursor RNA is designated SEQ

ID:452, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:452 is located at position 72494 relative to the genome of Autographa Californica Nucleopolyhedrovirus.

[21516] VGAM466 precursor RNA folds onto itself, forming VGAM466 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21517] An enzyme complex designated DICER COMPLEX, `dices` the VGAM466 folded precursor RNA into VGAM466 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 89%) nucleotide sequence of VGAM466 RNA is designated SEQ ID:3177, and is provided hereinbelow with reference to the sequence

listing part.

[21518] VGAM466 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM466 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM466 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21519] VGAM466 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM466 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM466 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM466 RNA, herein designated VGAM RNA, may



have a different number of host target binding sites in untranslated regions of a VGAM466 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21520] The complementary binding of VGAM466 RNA, herein designated VGAM RNA, to host target binding sites on VGAM466 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM466 host target RNA into VGAM466 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21521] It is appreciated that VGAM466 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM466 host target genes. The mRNA of each one of this plurality of VGAM466 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM466 RNA, herein designated VGAM

RNA, and which when bound by VGAM466 RNA causes inhibition of translation of respective one or more VGAM466 host target proteins.

[21522] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM466 gene, herein designated VGAM GENE, on one or more VGAM466 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21523] It is yet further appreciated that a function of VGAM466 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM466 include diagnosis, prevention and treatment of viral infection by Autographa Californica Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM466 correlate with, and may be deduced from, the identity of the host target genes which VGAM466 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21524] Nucleotide sequences of the VGAM466 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM466 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM466 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM466 are further described hereinbelow with reference to Table 1.

[21525] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM466 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM466 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21526] As mentioned hereinabove with reference to Fig. 1, a function of VGAM466 gene, herein designated VGAM is

inhibition of expression of VGAM466 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM466 correlate with, and may be deduced from, the identity of the target genes which VGAM466 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21527] B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633) is a VGAM466 host target gene. BCL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2 BINDING SITE, designated SEQ ID:6256, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21528] A function of VGAM466 is therefore inhibition of B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633). Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL2. B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993) is another VGAM466 host target gene. BCL7A BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by BCL7A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL7A BINDING SITE, designated SEQ ID:21988, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21529] Another function of VGAM466 is therefore inhibition of B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993). Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL7A. BCLG (Accession NM\_030766) is another VGAM466 host target gene. BCLG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCLG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCLG BINDING SITE, designated SEQ ID:25052, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21530] Another function of VGAM466 is therefore inhibition of

BCLG (Accession NM\_030766). Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCLG. Norrie Disease (pseudoglioma) (NDP, Accession NM\_000266) is another VGAM466 host target gene. NDP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NDP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDP BINDING SITE, designated SEQ ID:5809, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21531] Another function of VGAM466 is therefore inhibition of Norrie Disease (pseudoglioma) (NDP, Accession NM\_000266), a gene which may be involved in a pathway that regulates neural cell differentiation and proliferation. Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDP. The function of NDP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM113.Trichorhinophalangeal Syndrome I (TRPS1, Accession NM\_014112) is another VGAM466 host target gene. TRPS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPS1 BINDING SITE, designated SEQ ID:15361, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21532] Another function of VGAM466 is therefore inhibition of Trichorhinophalangeal Syndrome I (TRPS1, Accession NM\_014112), a gene which may function as a transcriptional activator protein. Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPS1. The function of TRPS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM172.FLJ12595 (Accession NM\_024994) is another VGAM466 host target gene. FLJ12595 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by FLJ12595, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12595 BINDING SITE, designated SEQ ID:24558, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21533] Another function of VGAM466 is therefore inhibition of FLJ12595 (Accession NM\_024994). Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12595. KIAA1078 (Accession XM\_036589) is another VGAM466 host target gene. KIAA1078 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1078 BINDING SITE, designated SEQ ID:32473, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21534] Another function of VGAM466 is therefore inhibition of KIAA1078 (Accession XM\_036589). Accordingly, utilities



of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1078. Proteasome (prosome, macropain) Inhibitor Subunit 1 (PI31) (PSMF1, Accession NM\_006814) is another VGAM466 host target gene. PSMF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSMF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSMF1 BINDING SITE, designated SEQ ID:13690, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21535] Another function of VGAM466 is therefore inhibition of Proteasome (prosome, macropain) Inhibitor Subunit 1 (PI31) (PSMF1, Accession NM\_006814). Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSMF1. LOC144195 (Accession XM\_016498) is another VGAM466 host target gene. LOC144195 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144195, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144195 BINDING SITE, designated SEQ ID:30266, to the nucleotide sequence of VGAM466 RNA, herein designated VGAM RNA, also designated SEQ ID:3177.

[21536] Another function of VGAM466 is therefore inhibition of LOC144195 (Accession XM\_016498). Accordingly, utilities of VGAM466 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144195. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 467 (VGAM467) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21537] VGAM467 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM467 was detected is described hereinabove with reference to Figs. 1–8.

[21538] VGAM467 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Autographa Californica Nucleopolyhedrovirus. VGAM467 host target gene, herein

designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21539] VGAM467 gene encodes a VGAM467 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM467 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM467 precursor RNA is designated SEQ ID:453, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:453 is located at position 73764 relative to the genome of Autographa Californica Nucleopolyhedrovirus.

[21540] VGAM467 precursor RNA folds onto itself, forming VGAM467 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21541] An enzyme complex designated DICER COMPLEX, `dices` the VGAM467 folded precursor RNA into VGAM467 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM467 RNA is designated SEQ ID:3178, and is provided hereinbelow with reference to the sequence listing part.

[21542] VGAM467 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM467 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM467 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21543] VGAM467 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM467 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM467 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM467 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM467 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21544] The complementary binding of VGAM467 RNA, herein designated VGAM RNA, to host target binding sites on VGAM467 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM467 host target RNA into VGAM467 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[21545] It is appreciated that VGAM467 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM467 host target genes. The mRNA of each one of this plurality of VGAM467 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM467 RNA, herein designated VGAM RNA, and which when bound by VGAM467 RNA causes inhibition of translation of respective one or more VGAM467 host target proteins.

[21546] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM467 gene, herein designated VGAM GENE, on one or more VGAM467 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21547] It is yet further appreciated that a function of VGAM467 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of viral infection by Autographa Californica Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM467 correlate with, and may be deduced from, the identity of the host target genes which VGAM467 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21548] Nucleotide sequences of the VGAM467 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM467 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM467 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM467 are further described hereinbelow with reference to Table 1.

[21549] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM467 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM467 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21550] As mentioned hereinabove with reference to Fig. 1, a function of VGAM467 gene, herein designated VGAM is inhibition of expression of VGAM467 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM467 correlate with, and may be deduced from, the identity of the target genes which VGAM467 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21551] Neural Precursor Cell Expressed, Developmentally Down-regulated 4 (NEDD4, Accession XM\_046129) is a VGAM467 host target gene. NEDD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEDD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEDD4 BINDING SITE, designated SEQ ID:34693, to the nucleotide sequence of



VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21552] A function of VGAM467 is therefore inhibition of Neural Precursor Cell Expressed, Developmentally Down-regulated 4 (NEDD4, Accession XM\_046129), a gene which ubiquitinates regulatory proteins involved in transcription. Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEDD4. The function of NEDD4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM209. Transmembrane, Prostate Androgen Induced RNA (TMEPAI, Accession NM\_020182) is another VGAM467 host target gene. TMEPAI BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMEPAI, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMEPAI BINDING SITE, designated SEQ ID:21405, to the nucleotide sequence of VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21553] Another function of VGAM467 is therefore inhibition of Transmembrane, Prostate Androgen Induced RNA (TMEPAI, Accession NM\_020182). Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMEPAI. DKFZp761G2113 (Accession XM\_046017) is another VGAM467 host target gene. DKFZp761G2113 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZp761G2113, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761G2113 BINDING SITE, designated SEQ ID:34642, to the nucleotide sequence of VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21554] Another function of VGAM467 is therefore inhibition of DKFZp761G2113 (Accession XM\_046017). Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761G2113. FLJ12517 (Accession NM\_023007) is another VGAM467 host target gene. FLJ12517 BINDING SITE is HOST TARGET binding site found in the 3` un-

translated region of mRNA encoded by FLJ12517, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12517 BINDING SITE, designated SEQ ID:23270, to the nucleotide sequence of VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21555] Another function of VGAM467 is therefore inhibition of FLJ12517 (Accession NM\_023007). Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12517. MGC15437 (Accession NM\_032873) is another VGAM467 host target gene. MGC15437 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC15437, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15437 BINDING SITE, designated SEQ ID:26688, to the nucleotide sequence of VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21556] Another function of VGAM467 is therefore inhibition of MGC15437 (Accession NM\_032873). Accordingly, utilities

of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15437. LOC144893 (Accession XM\_096687) is another VGAM467 host target gene. LOC144893 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC144893, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144893 BINDING SITE, designated SEQ ID:40458, to the nucleotide sequence of VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21557] Another function of VGAM467 is therefore inhibition of LOC144893 (Accession XM\_096687). Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144893. LOC221596 (Accession XM\_166331) is another VGAM467 host target gene. LOC221596 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221596, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC221596 BINDING SITE, designated SEQ ID:44174, to the nucleotide sequence of VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21558] Another function of VGAM467 is therefore inhibition of LOC221596 (Accession XM\_166331). Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221596. LOC57821 (Accession NM\_021179) is another VGAM467 host target gene. LOC57821 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC57821, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57821 BINDING SITE, designated SEQ ID:22151, to the nucleotide sequence of VGAM467 RNA, herein designated VGAM RNA, also designated SEQ ID:3178.

[21559] Another function of VGAM467 is therefore inhibition of LOC57821 (Accession NM\_021179). Accordingly, utilities of VGAM467 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57821. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 468 (VGAM468) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21560] VGAM468 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM468 was detected is described hereinabove with reference to Figs. 1–8.

[21561] VGAM468 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 2. VGAM468 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21562] VGAM468 gene encodes a VGAM468 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM468 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM468 precursor RNA is designated SEQ ID:454, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:454 is located at position 33653 relative to the genome of

## Equine Herpesvirus 2.

[21563] VGAM468 precursor RNA folds onto itself, forming VGAM468 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21564] An enzyme complex designated DICER COMPLEX, `dices` the VGAM468 folded precursor RNA into VGAM468 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM468 RNA is designated SEQ ID:3179, and is provided hereinbelow with reference to the sequence listing part.

[21565] VGAM468 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM468 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM468 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21566] VGAM468 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM468 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM468 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM468 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM468 host target RNA, herein designated VGAM HOST TARGET RNA. It is further



appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21567] The complementary binding of VGAM468 RNA, herein designated VGAM RNA, to host target binding sites on VGAM468 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM468 host target RNA into VGAM468 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21568] It is appreciated that VGAM468 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM468 host target genes. The mRNA of each one of this plurality of VGAM468 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM468 RNA, herein designated VGAM RNA, and which when bound by VGAM468 RNA causes inhibition of translation of respective one or more VGAM468 host target proteins.

[21569] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM468 gene, herein designated VGAM GENE, on one or more VGAM468 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21570] It is yet further appreciated that a function of VGAM468 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM468 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM468 cor-

relate with, and may be deduced from, the identity of the host target genes which VGAM468 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21571] Nucleotide sequences of the VGAM468 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM468 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM468 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM468 are further described hereinbelow with reference to Table 1.

[21572] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM468 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM468 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21573] As mentioned hereinabove with reference to Fig. 1, a function of VGAM468 gene, herein designated VGAM is inhibition of expression of VGAM468 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM468 correlate with, and may be deduced

from, the identity of the target genes which VGAM468 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21574] RAB20, Member RAS Oncogene Family (RAB20, Accession NM\_017817) is a VGAM468 host target gene. RAB20 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB20, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB20 BINDING SITE, designated SEQ ID:19462, to the nucleotide sequence of VGAM468 RNA, herein designated VGAM RNA, also designated SEQ ID:3179.

[21575] A function of VGAM468 is therefore inhibition of RAB20, Member RAS Oncogene Family (RAB20, Accession NM\_017817). Accordingly, utilities of VGAM468 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB20. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 469 (VGAM469) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host

target genes is known in the art.

[21576] VGAM469 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM469 was detected is described hereinabove with reference to Figs. 1–8.

[21577] VGAM469 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 2. VGAM469 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21578] VGAM469 gene encodes a VGAM469 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM469 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM469 precursor RNA is designated SEQ ID:455, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:455 is located at position 156830 relative to the genome of Equine Herpesvirus 2.

[21579] VGAM469 precursor RNA folds onto itself, forming VGAM469 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[21580] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM469 folded precursor RNA into VGAM469 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 42%) nucleotide se-  
quence of VGAM469 RNA is designated SEQ ID:3180, and  
is provided hereinbelow with reference to the sequence  
listing part.

[21581] VGAM469 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM469 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM469 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[21582] VGAM469 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM469 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM469 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM469 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM469 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5' UTR regions.

[21583] The complementary binding of VGAM469 RNA, herein designated VGAM RNA, to host target binding sites on VGAM469 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM469 host target RNA into VGAM469 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21584] It is appreciated that VGAM469 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM469 host target genes. The mRNA of each one of this plurality of VGAM469 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM469 RNA, herein designated VGAM RNA, and which when bound by VGAM469 RNA causes inhibition of translation of respective one or more VGAM469 host target proteins.

[21585] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM469 gene, herein designated VGAM GENE, on one or



more VGAM469 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21586] It is yet further appreciated that a function of VGAM469 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM469 correlate with, and may be deduced from, the identity of the host target genes which VGAM469 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [21587] Nucleotide sequences of the VGAM469 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM469 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM469 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM469 are further described hereinbelow with reference to Table 1.
- [21588] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM469 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM469 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21589] As mentioned hereinabove with reference to Fig. 1, a function of VGAM469 gene, herein designated VGAM is inhibition of expression of VGAM469 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM469 correlate with, and may be deduced from, the identity of the target genes which VGAM469 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [21590] Chaperone, ABC1 Activity of Bc1 Complex Like (*S. pombe*)

(CABC1, Accession NM\_020247) is a VGAM469 host target gene. CABC1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CABC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CABC1 BINDING SITE, designated SEQ ID:21541, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21591] A function of VGAM469 is therefore inhibition of Chaperone, ABC1 Activity of Bc1 Complex Like (*S. pombe*) (CABC1, Accession NM\_020247). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CABC1. F-box and Leucine-rich Repeat Protein 11 (FBXL11, Accession NM\_012308) is another VGAM469 host target gene. FBXL11 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FBXL11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXL11 BINDING SITE, designated SEQ

ID:14682, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21592] Another function of VGAM469 is therefore inhibition of F-box and Leucine-rich Repeat Protein 11 (FBXL11, Accession NM\_012308), a gene which are BTB/POZ domain-containing zinc finger proteins implicated in oncogenesis. Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXL11. The function of FBXL11 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM404. Mitogen-activated Protein Kinase Kinase Kinase 1 (MAP3K1, Accession XM\_042066) is another VGAM469 host target gene. MAP3K1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MAP3K1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP3K1 BINDING SITE, designated SEQ ID:33682, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3180.

[21593] Another function of VGAM469 is therefore inhibition of Mitogen-activated Protein Kinase Kinase Kinase 1 (MAP3K1, Accession XM\_042066), a gene which can phosphorylate and activate mapkk 1 and mapkk 2 (mek1/mek2) which leads to phosphorylation of map kinases. it is also a highly efficient activator of the jnk cascade. Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP3K1. The function of MAP3K1 has been established by previous studies. Gamma interferon (IFNG; 147570) induces a number of genes, including MEKK1, to upregulate cellular responses by using specific transcription factors and the cognate elements (Roy et al., 2002). Lu et al. (2002) found that the PHD domain of MEKK1, a RING finger-like structure, exhibited E3 ubiquitin ligase activity toward ERK2 (OMIM Ref. No. 176948) in vitro and in vivo. Moreover, both MEKK1 kinase activity and the docking motif on ERK1 (OMIM Ref. No. 601795)/ERK2 were involved in ERK1/ERK2 ubiquitination. Significantly, cells expressing ERK2 with the docking motif mutation were resistant to sorbitol-induced apoptosis. Therefore, MEKK1 functions not only as an upstream acti-

vator of ERK and JNK (see OMIM Ref. No. 601158) through its kinase domain, but also as an E3 ligase through its PHD domain, providing a negative regulatory mechanism for decreasing ERK1/ERK2 activity. Animal model experiments lend further support to the function of MAP3K1. Yujiri et al. (1998) targeted disruption of the gene encoding Mekk1 to define its function in the regulation of MAP kinase pathways and cell survival. Mekk1  $-/-$  embryonic stem cells from mice had lost or altered responses of Jnk to microtubule disruption and cold stress but activated Jnk normally in response to heat shock, anisomycin, and ultraviolet irradiation. Activation of Jnk was lost and that of Erk was diminished in response to hyperosmolarity and serum factors in Mekk1  $-/-$  cells. Loss of Mekk1 expression resulted in a greater apoptotic response of cells to hyperosmolarity and microtubule disruption. When activated by specific stresses that alter cell shape and the cytoskeleton, Mekk1 signals to protect cells from apoptosis

[21594] It is appreciated that the abovementioned animal model for MAP3K1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21595] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [21596] Lu, Z.; Xu, S.; Joazeiro, C.; Cobb, M. H.; Hunter, T. : The PHD domain of MEKK1 acts as an E3 ubiquitin ligase and mediates ubiquitination and degradation of ERK1/2. Molec. Cell 9: 945–956, 2002. ; and
- [21597] Yujiri, T.; Sather, S.; Fanger, G. R.; Johnson, G. L. : Role of MEKK1 in cell survival and activation of JNK and ERK pathways defined by targeted gene disruption. Science 282: 1911–1914, 1.
- [21598] Further studies establishing the function and utilities of MAP3K1 are found in John Hopkins OMIM database record ID 600982, and in cited publications numbered 781 and 7884–7885 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. AWP1 (Accession NM\_019006) is another VGAM469 host target gene. AWP1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by AWP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AWP1 BINDING SITE, designated SEQ ID:21078, to the nucleotide sequence of VGAM469 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3180.

[21599] Another function of VGAM469 is therefore inhibition of AWP1 (Accession NM\_019006). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AWP1. DCNP1 (Accession NM\_130848) is another VGAM469 host target gene. DCNP1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DCNP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DCNP1 BINDING SITE, designated SEQ ID:28385, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21600] Another function of VGAM469 is therefore inhibition of DCNP1 (Accession NM\_130848). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DCNP1. DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 34 (DDX34, Accession NM\_014681) is another VGAM469 host target gene. DDX34 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA en-



coded by DDX34, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDX34 BINDING SITE, designated SEQ ID:16163, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21601] Another function of VGAM469 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 34 (DDX34, Accession NM\_014681). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDX34. DREV1 (Accession NM\_016025) is another VGAM469 host target gene. DREV1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DREV1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DREV1 BINDING SITE, designated SEQ ID:18108, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21602] Another function of VGAM469 is therefore inhibition of

DREV1 (Accession NM\_016025). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DREV1. FLJ10209 (Accession NM\_018026) is another VGAM469 host target gene. FLJ10209 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10209, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10209 BINDING SITE, designated SEQ ID:19768, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21603] Another function of VGAM469 is therefore inhibition of FLJ10209 (Accession NM\_018026). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10209. FLJ20401 (Accession NM\_017805) is another VGAM469 host target gene. FLJ20401 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20401, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ20401 BINDING SITE, designated SEQ ID:19448, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21604] Another function of VGAM469 is therefore inhibition of FLJ20401 (Accession NM\_017805). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20401. FLJ22529 (Accession NM\_024789) is another VGAM469 host target gene. FLJ22529 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22529, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22529 BINDING SITE, designated SEQ ID:24170, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21605] Another function of VGAM469 is therefore inhibition of FLJ22529 (Accession NM\_024789). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22529. LCHN (Accession XM\_098615) is another VGAM469 host

target gene. LCHN BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LCHN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LCHN BINDING SITE, designated SEQ ID:41729, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21606] Another function of VGAM469 is therefore inhibition of LCHN (Accession XM\_098615). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LCHN. MGC3113 (Accession NM\_024035) is another VGAM469 host target gene. MGC3113 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC3113, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC3113 BINDING SITE, designated SEQ ID:23469, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21607] Another function of VGAM469 is therefore inhibition of MGC3113 (Accession NM\_024035). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC3113. Mucin 16 (MUC16, Accession XM\_018353) is another VGAM469 host target gene. MUC16 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MUC16, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MUC16 BINDING SITE, designated SEQ ID:30356, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21608] Another function of VGAM469 is therefore inhibition of Mucin 16 (MUC16, Accession XM\_018353). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MUC16. Myosin, Heavy Polypeptide 7B, Cardiac Muscle, Beta (MYH7B, Accession XM\_047196) is another VGAM469 host target gene. MYH7B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYH7B, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYH7B BINDING SITE, designated SEQ ID:34909, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21609] Another function of VGAM469 is therefore inhibition of Myosin, Heavy Polypeptide 7B, Cardiac Muscle, Beta (MYH7B, Accession XM\_047196). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYH7B. PCTAIRE2BP (Accession XM\_047341) is another VGAM469 host target gene. PCTAIRE2BP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PCTAIRE2BP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCTAIRE2BP BINDING SITE, designated SEQ ID:34952, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21610] Another function of VGAM469 is therefore inhibition of PCTAIRE2BP (Accession XM\_047341). Accordingly, utilities

of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PC-TAIRE2BP. SEC8 (Accession NM\_021807) is another VGAM469 host target gene. SEC8 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SEC8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC8 BINDING SITE, designated SEQ ID:22362, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21611] Another function of VGAM469 is therefore inhibition of SEC8 (Accession NM\_021807). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEC8. SIMRP7 (Accession XM\_166462) is another VGAM469 host target gene. SIMRP7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SIMRP7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIMRP7 BINDING SITE, designated

SEQ ID:44372, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21612] Another function of VGAM469 is therefore inhibition of SIMRP7 (Accession XM\_166462). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIMRP7. SS-56 (Accession XM\_006063) is another VGAM469 host target gene. SS-56 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SS-56, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SS-56 BINDING SITE, designated SEQ ID:29990, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21613] Another function of VGAM469 is therefore inhibition of SS-56 (Accession XM\_006063). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SS-56. LOC222962 (Accession XM\_167291) is another VGAM469 host target gene. LOC222962 BINDING SITE is HOST TAR-



GET binding site found in the 3' untranslated region of mRNA encoded by LOC222962, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222962 BINDING SITE, designated SEQ ID:44631, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21614] Another function of VGAM469 is therefore inhibition of LOC222962 (Accession XM\_167291). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222962. LOC255975 (Accession XM\_171083) is another VGAM469 host target gene. LOC255975 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255975, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255975 BINDING SITE, designated SEQ ID:45889, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21615] Another function of VGAM469 is therefore inhibition of

LOC255975 (Accession XM\_171083). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255975. LOC256401 (Accession XM\_171149) is another VGAM469 host target gene. LOC256401 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256401, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256401 BINDING SITE, designated SEQ ID:45947, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21616] Another function of VGAM469 is therefore inhibition of LOC256401 (Accession XM\_171149). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256401. LOC90249 (Accession XM\_030300) is another VGAM469 host target gene. LOC90249 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90249, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of LOC90249 BINDING SITE, designated SEQ ID:31014, to the nucleotide sequence of VGAM469 RNA, herein designated VGAM RNA, also designated SEQ ID:3180.

[21617] Another function of VGAM469 is therefore inhibition of LOC90249 (Accession XM\_030300). Accordingly, utilities of VGAM469 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90249. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 470 (VGAM470) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21618] VGAM470 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM470 was detected is described hereinabove with reference to Figs. 1–8.

[21619] VGAM470 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM470 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in

the human genome.

[21620] VGAM470 gene encodes a VGAM470 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM470 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM470 precursor RNA is designated SEQ ID:456, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:456 is located at position 45550 relative to the genome of African Swine Fever Virus.

[21621] VGAM470 precursor RNA folds onto itself, forming VGAM470 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21622] An enzyme complex designated DICER COMPLEX, `dices` the VGAM470 folded precursor RNA into VGAM470 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM470 RNA is designated SEQ ID:3181, and is provided hereinbelow with reference to the sequence listing part.

[21623] VGAM470 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM470 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM470 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21624] VGAM470 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM470 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM470 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM470 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM470 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21625] The complementary binding of VGAM470 RNA, herein designated VGAM RNA, to host target binding sites on VGAM470 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM470 host target RNA into VGAM470 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21626] It is appreciated that VGAM470 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM470 host target genes. The mRNA of each one of this plurality of VGAM470 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM470 RNA, herein designated VGAM RNA, and which when bound by VGAM470 RNA causes inhibition of translation of respective one or more VGAM470 host target proteins.

[21627] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM470 gene, herein designated VGAM GENE, on one or more VGAM470 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21628] It is yet further appreciated that a function of VGAM470 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM470 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus. Specific functions, and accordingly utilities, of VGAM470 correlate with, and may be deduced from, the identity of the host target genes which VGAM470 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21629] Nucleotide sequences of the VGAM470 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM470 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM470 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM470 are further described hereinbelow with reference to Table 1.

[21630] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of



Fig. 1, found on VGAM470 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM470 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21631] As mentioned hereinabove with reference to Fig. 1, a function of VGAM470 gene, herein designated VGAM is inhibition of expression of VGAM470 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM470 correlate with, and may be deduced from, the identity of the target genes which VGAM470 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21632] Epilepsy, Progressive Myoclonus Type 2, Lafora Disease (laforin) (EPM2A, Accession NM\_005670) is a VGAM470 host target gene. EPM2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPM2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPM2A BINDING SITE, designated SEQ ID:12228, to the nucleotide sequence of VGAM470 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3181.

[21633] A function of VGAM470 is therefore inhibition of Epilepsy, Progressive Myoclonus Type 2, Lafora Disease (laforin) (EPM2A, Accession NM\_005670), a gene which Laforin; protein tyrosine phosphatase that may have role in glycogen metabolism. Accordingly, utilities of VGAM470 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPM2A. The function of EPM2A has been established by previous studies. In the Lafora type, onset takes the form of grand mal seizures and/or myoclonus at about age 15 years. Rapid and severe mental deterioration ensues, often with psychotic features. Survival is short, less than 10 years after onset. Histologic study of the brain shows Lafora bodies (which may also be demonstrable on muscle and liver biopsy). Intracellular Lafora bodies suggesting amyloid are found in the brain, and similar inclusions in the cells of the heart and liver (Harriman and Millar, 1955). The Lafora material has the properties of an acid mucopolysaccharide. Yokoi et al. (1968) arrived at a preliminary conclusion that the Lafora body is polyglucosan in nature. They pictured the existence of an enzyme defect which leads to deposition of polyglucosans near their site of synthesis in the agran-

ular endoplasmic reticulum. Schwarz and Yanoff (1965) described a brother and sister, offspring of a one-and-one-half cousin marriage, with this disease. Seizures began at age 15 in the boy with slowly progressive motor and mental deterioration leading to death at age 23.5 years. The sister's seizures began at age 14 years and progression to dementia and blindness occurred, with death at age 19. Intra- and extracellular Lafora bodies were found in the CNS, retina, axis cylinders of spinal nerves, heart muscle, liver cells, and striated muscle fibers. Diagnosis by liver or muscle biopsy was proposed. Busard et al. (1986, 1987) demonstrated that the diagnosis can be made reliably on axillary skin biopsy; all patients show typical periodic acid-Schiff (PAS)-positive inclusions in the myoepithelial cells of the secretory acini of the apocrine glands and/or in the cells of the eccrine duct. The method has no value for carrier detection. In cultured fibroblasts, Fluharty et al. (1970) described bodies which may be the equivalent of the Lafora body observed histologically. Sarlin et al. (1960) claimed that electroencephalographic abnormalities distinguished heterozygotes from homozygous normals. Norio and Koskiniemi (1979), as well as others, have concluded that there are 3 types of

what they termed progressive myoclonic epilepsy (PME). The Lafora type shows onset of grand mal seizures and/or myoclonus around the fifteenth year of life; rapid and severe mental deterioration, often with psychotic symptoms; short survival; histologic finding of Lafora bodies; and autosomal recessive inheritance. The Unverricht–Lundborg type (EPM1; 254800), which is frequent in Finland, has onset around the tenth year; variable severity; progressive incapacitation from myoclonus associated with mild mental symptoms; variable survival; 'degenerative' histologic changes; and autosomal recessive inheritance. A dominant form, to which Hartung's name is attached (see OMIM Ref. No. 159600), has been described. By linkage studies in 3 Italian families with Lafora disease, Lehesjoki et al. (1992) demonstrated that the gene is located at a locus other than that for the Unverricht–Lundborg type on chromosome 21q22.3. Serratosa et al. (1995) studied linkage in 9 families in which Lafora disease had been proven by biopsy in at least 1 member. Using microsatellite markers spaced an average of 13 cM apart, they used linkage analysis in all 9 families and homozygosity mapping in 4 consanguineous families to assign the gene for Lafora disease to 6q23–q25. An extended pedigree with 5 affected

members independently proved linkage. The multipoint 1-lod unit support interval covered a 2.5-cM region surrounding D6S403. Homozygosity mapping defined a 17-cM region in 6q23-q25 flanked by D6S292 and D6S420. The 9 families with a total of 19 patients affected with Lafora disease originated from the United States, Spain, Palestine, and Iran. Maddox et al. (1997) studied a 2-generation family in which a recombination event reduced the Lafora critical region to a 4-cM interval flanked by markers D6S308 and D6S311. Sainz et al. (1997) narrowed the assignment of the MELF locus within 6q24 by study of recombinants and homozygosities. Ganesh et al. (2000) cloned and expressed the full-length 38-kD laforin protein in transfected cells. Recombinant laforin was able to hydrolyze phosphotyrosine as well as phosphoserine/threonine substrates, demonstrating that laforin is an active dual-specificity phosphatase. Biochemical, immunofluorescence, and ultrastructural studies on transfected HeLa cells revealed that laforin is a cytoplasmic protein associated with polyribosomes. Expression of 2 proteins with missense mutations seen in EPM2A patients resulted in ubiquitin-positive perinuclear aggregates, suggesting that these were misfolded proteins targeted for degradation.

The authors suggested that laforin is involved in translational regulation and that protein misfolding may be one of the molecular bases of the Lafora disease phenotype caused by missense mutations in the EPM2A gene.

Gomez-Garre et al. (2000) reported the complete coding sequence of the EPM2A gene, including the ATG initiation codon region. They used SSCP analysis of the 4 exons in 34 unrelated patients with Lafora disease and identified EPM2A mutations in 27 (79%) of them (49 of 68 chromosomes, or 72%). The patients originated from Spain, Italy, Australia, Holland, the US, North Africa, Turkey, and France. A total of 20 different EPM2A mutations, 11 of them novel, were characterized. The authors summarized 25 EPM2A mutations distributed throughout the gene in 44 unrelated Lafora disease patients. The mutations included 10 deletions of different sizes, 9 missense mutations, 3 nonsense mutations, and 3 frameshift mutations. The R241X mutation (254780.0008) was encountered in almost 40% of the probands. In 5 Lafora disease families (13% of the families studied), Gomez-Garre et al. (2000) excluded linkage to the EPM2A gene region.

[21634] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [21635] Norio, R.; Koskiniemi, M. : Progressive myoclonus epilepsy: genetic and nosological aspects with special reference to 107 Finnish patients. Clin. Genet. 15: 382–398, 1979. ; and
- [21636] Gomez–Garre, P.; Sanz, Y.; Rodriguez de Cordoba, S.; Ser-ratosa, J. M. : Mutational spectrum of the EPM2A gene in progressive myoclonus epilepsy of Lafora: high degree of allelic heterogen.
- [21637] Further studies establishing the function and utilities of EPM2A are found in John Hopkins OMIM database record ID 254780, and in cited publications numbered 9099–9107, 9220–922 and 9229–9228 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA1493 (Accession XM\_034415) is another VGAM470 host target gene. KIAA1493 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1493, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1493 BINDING SITE, designated SEQ ID:32094, to the nucleotide sequence of VGAM470 RNA, herein designated

VGAM RNA, also designated SEQ ID:3181.

[21638] Another function of VGAM470 is therefore inhibition of KIAA1493 (Accession XM\_034415). Accordingly, utilities of VGAM470 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1493. KR18 (Accession NM\_033288) is another VGAM470 host target gene. KR18 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KR18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KR18 BINDING SITE, designated SEQ ID:27119, to the nucleotide sequence of VGAM470 RNA, herein designated VGAM RNA, also designated SEQ ID:3181.

[21639] Another function of VGAM470 is therefore inhibition of KR18 (Accession NM\_033288). Accordingly, utilities of VGAM470 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KR18. LOC169166 (Accession XM\_095541) is another VGAM470 host target gene. LOC169166 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC169166, corresponding to a HOST



TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169166 BINDING SITE, designated SEQ ID:40272, to the nucleotide sequence of VGAM470 RNA, herein designated VGAM RNA, also designated SEQ ID:3181.

[21640] Another function of VGAM470 is therefore inhibition of LOC169166 (Accession XM\_095541). Accordingly, utilities of VGAM470 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC169166. LOC200301 (Accession XM\_114197) is another VGAM470 host target gene. LOC200301 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200301 BINDING SITE, designated SEQ ID:42783, to the nucleotide sequence of VGAM470 RNA, herein designated VGAM RNA, also designated SEQ ID:3181.

[21641] Another function of VGAM470 is therefore inhibition of LOC200301 (Accession XM\_114197). Accordingly, utilities of VGAM470 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC200301. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 471 (VGAM471) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21642] VGAM471 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM471 was detected is described hereinabove with reference to Figs. 1–8.

[21643] VGAM471 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 6. VGAM471 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21644] VGAM471 gene encodes a VGAM471 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM471 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM471 precursor RNA is designated SEQ

ID:457, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:457 is located at position 135287 relative to the genome of Human Herpesvirus 6.

[21645] VGAM471 precursor RNA folds onto itself, forming VGAM471 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21646] An enzyme complex designated DICER COMPLEX, `dices` the VGAM471 folded precursor RNA into VGAM471 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 83%) nucleotide sequence of VGAM471 RNA is designated SEQ ID:3182, and is provided hereinbelow with reference to the sequence

listing part.

[21647] VGAM471 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM471 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM471 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21648] VGAM471 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM471 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM471 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM471 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM471 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21649] The complementary binding of VGAM471 RNA, herein designated VGAM RNA, to host target binding sites on VGAM471 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM471 host target RNA into VGAM471 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21650] It is appreciated that VGAM471 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM471 host target genes. The mRNA of each one of this plurality of VGAM471 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM471 RNA, herein designated VGAM

RNA, and which when bound by VGAM471 RNA causes inhibition of translation of respective one or more VGAM471 host target proteins.

[21651] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM471 gene, herein designated VGAM GENE, on one or more VGAM471 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21652] It is yet further appreciated that a function of VGAM471 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM471 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 6. Specific functions, and accordingly utilities, of VGAM471 correlate with, and may be deduced from, the identity of the host target genes which VGAM471 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21653] Nucleotide sequences of the VGAM471 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM471 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM471 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM471 are further described hereinbelow with reference to Table 1.

[21654] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM471 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM471 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21655] As mentioned hereinabove with reference to Fig. 1, a function of VGAM471 gene, herein designated VGAM is

inhibition of expression of VGAM471 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM471 correlate with, and may be deduced from, the identity of the target genes which VGAM471 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21656] Bone Morphogenetic Protein 1 (BMP1, Accession NM\_006131) is a VGAM471 host target gene. BMP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BMP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BMP1 BINDING SITE, designated SEQ ID:12770, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21657] A function of VGAM471 is therefore inhibition of Bone Morphogenetic Protein 1 (BMP1, Accession NM\_006131), a gene which cleaves procollagens leading to formation of extracellular matrix. Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BMP1. The function of BMP1 and its association with various diseases and clinical



conditions, has been established by previous studies, as described hereinabove with reference to VGAM247.Dihydropyrimidinase-like 2 (DPYSL2, Accession NM\_001386) is another VGAM471 host target gene. DPYSL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DPYSL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DPYSL2 BINDING SITE, designated SEQ ID:7061, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21658] Another function of VGAM471 is therefore inhibition of Dihydropyrimidinase-like 2 (DPYSL2, Accession NM\_001386), a gene which is a member of the dihydropyrimidinase family. Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DPYSL2. The function of DPYSL2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM217.Inhibitor of Kappa Light Polypeptide Gene En-

hancer In B-cells, Kinase Gamma (IKBKG, Accession NM\_003639) is another VGAM471 host target gene. IKBKG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IKBKG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IKBKG BINDING SITE, designated SEQ ID:9711, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21659] Another function of VGAM471 is therefore inhibition of Inhibitor of Kappa Light Polypeptide Gene Enhancer In B-cells, Kinase Gamma (IKBKG, Accession NM\_003639), a gene which regulatory subunit part of the ikk-signalosome complex activation. also considered to be a mediator for tax activation of nf-kappa-b. could be implicated in nf-kappa-b-mediated protection from cytokine toxicity. Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IKBKG. The function of IKBKG has been established by previous studies. Yamaoka et al. (1998) characterized a mutant cell line, 5R, originally isolated as a cellular flat variant of Rat-1 fibroblasts trans-

formed by the Tax protein of human T-cell leukemia virus type 1 (OMIM Ref. No. HTLV-1). The 5R cell line was unresponsive to all tested NF-kappa-B (NFKB; OMIM Ref. No. 164011)-activating stimuli. Using a genetic complementation approach, Yamaoka et al. (1998) cloned a component of the I-kappa-B kinase complex that they termed NEMO for 'NF-kappa-B essential modulator' from 5R cells. The 2.8-kb NEMO cDNA encodes a 412-amino acid protein that is acidic, rich in glutamic acid and glutamine residues (each 13%), and contains a leucine zipper motif at amino acids 315-342. Yamaoka et al. (1998) determined that the defective phenotype of 5R cells resulted from the absence of the NEMO protein. NEMO also complemented the 1.3E2 mutant cell line, in which NFKB is not activated in response to a large set of stimuli. NEMO interacted with IKK2 (IKK-beta; 603258), but not with IKK1 (IKK-alpha; 600664). Aradhya et al. (2001) identified a truncated copy of NEMO (delta-NEMO), which maps 22 kb distal to NEMO and contains only exons 3 through 10. A sequence of 26 kb 3-prime of the NEMO coding sequence is also present in the same position relative to the delta-NEMO locus, bringing the total length of the duplication to 35.5 kb. The LAGE2 gene is also located within this dupli-

cated region, and a similar but unique LAGE1 gene is located just distal to the duplicated loci. Mapping and sequence information indicated that the duplicated regions are in opposite orientation. Analysis of the great apes suggested that the NEMO/LAGE2 duplication occurred after divergence of the lineage leading to present day humans, chimpanzees, and gorillas, 10 to 15 million years ago. Despite this substantial evolutionary history, only 22 single-nucleotide differences exist between the 2 copies over the entire 35.5 kb, making the duplications more than 99% identical. This high sequence identity and the inverted orientations of the 2 copies, along with duplications of smaller internal sections within each copy, predispose this region to various genomic alterations. Aradhya et al. (2001) detected 4 rearrangements that involved NEMO, delta-NEMO, or LAGE1 and LAGE2. The authors hypothesized that the susceptibility of this complex genomic region to various types of pathogenic and polymorphic rearrangements may underlie the recurrent lethal deletion associated with IP Animal model experiments lend further support to the function of IKBKG. Schmidt-Supprian et al. (2000) found that disruption of the mouse *Ikbkg* gene produces male embryonic lethality, completely

blocks NF-kappa-B activation by proinflammatory cytokines, and interferes with the generation and/or persistence of lymphocytes. Heterozygous female mice developed patchy skin lesions with massive granulocyte infiltration and hyperproliferation and increased apoptosis of keratinocytes. Diseased animals presented severe growth retardation and early mortality. Surviving mice recovered almost completely, presumably through clearing the skin of Ikbkg-deficient keratinocytes. The authors stated that male lethality and strikingly similar skin lesions in heterozygous females are hallmarks of the human genetic disorder IP2

[21660] It is appreciated that the abovementioned animal model for IKBKG is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21661] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21662] Schmidt-Supprian, M.; Bloch, W.; Courtois, G.; Addicks, K.; Israel, A.; Rajewsky, K.; Pasparakis, M. : NEMO/IKK-gamma-deficient mice model incontinentia pigmenti. Molec. Cell 5: 981-992, 2000. ; and

[21663] Aradhya, S.; Bardaro, T.; Galgoczy, P.; Yamagata, T.; Esposito, T.; Patlan, H.; Ciccodicola, A.; Munnich, A.; Kenwick, S.; Platzer, M.; D'Urso, M.; Nelson, D. L. : Multiple pathogenic.

[21664] Further studies establishing the function and utilities of IKBKG are found in John Hopkins OMIM database record ID 300248, and in cited publications numbered 9191–9192, 919 and 9195–9209 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Myeloma Overexpressed Gene (in a subset of t(11;14) Positive Multiple Myelomas) (MYEOV, Accession NM\_138768) is another VGAM471 host target gene. MYEOV BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MYEOV, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYEOV BINDING SITE, designated SEQ ID:29001, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21665] Another function of VGAM471 is therefore inhibition of Myeloma Overexpressed Gene (in a subset of t(11;14)

Positive Multiple Myelomas) (MYEOV, Accession NM\_138768), a gene which is encoded by MYELOMA OVEREXPRESSED GENE. Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYEOV. The function of MYEOV has been established by previous studies. By cloning gastric carcinoma tumor DNA into phage vectors, probing with human Alu repetitive sequences, and exon-trap analysis, Janssen et al. (2000) isolated a cDNA encoding MYEOV (myeloma overexpressed gene). Sequence analysis predicted that the 313-amino acid protein contains no known functional motifs except for an RNP1 motif typical of RNA-binding proteins and a leucine-isoleucine tail similar to cytoplasmically exposed membrane proteins with a C-terminal membrane anchor. Northern blot analysis detected a major 2.8-kb and a minor 3.5-kb transcript in various tumor cell lines. In 3 of 7 multiple myeloma cell lines with a t(11;14)(q13;q32) and cyclin D1 (CCND1; 168461) overexpression, Northern blot analysis determined that MYEOV was overexpressed. In all 7 cell lines, the breakpoint was mapped to the 360-kb region between the 2 genes. MYEOV overexpression was associated with the juxtaposition of an enhancer to the

MYEOV gene. Using FISH, Janssen et al. (2000) mapped the MYEOV gene to 11q13.1, 360 kb centromeric to CCND1. DNA amplifications at 11q13 are frequently observed in esophageal squamous cell carcinoma (OMIM Ref. No. 133239) and correlate with a malignant phenotype. Although this amplicon spans a region of several megabases and harbors numerous genes, CCND1 and EMS1 (OMIM Ref. No. 164765) are thought to be the relevant candidates in esophageal carcinoma. Janssen et al. (2002) investigated whether the putative transforming gene MYEOV, mapping 360 kb centromeric to CCND1 and activated concomitantly with CCND1 in a subset of t(11;14)(q13;q32) positive multiple myeloma cell lines, represents a target of 11q13 amplification in esophageal carcinoma. They tested 31 esophageal squamous cell carcinoma cell lines and 48 primary tumors for copy number levels of MYEOV and demonstrated that MYEOV was always coamplified with CCND1. However, its activation was sometimes inhibited by an epigenetic mechanism.

[21666] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21667] Janssen, J. W. G.; Imoto, I.; Inoue, J.; Shimada, Y.; Ueda,



M.; Imamura, M.; Bartram, C. R.; Inazawa, J. : MYEOV, a gene at 11q13, is coamplified with CCND1, but epigenetically inactivated in a subset of esophageal squamous cell carcinomas. J. Hum. Genet. 47: 460–464, 2002. ; and

[21668] Janssen, J. W. G.; Vaandrager, J.–W.; Heuser, T.; Jauch, A.; Kluin, P. M.; Geelen, E.; Bergsagel, P. L.; Kuehl, W. M.; Drexler, H. G.; Otsuki, T.; Bartram, C. R.; Schuuring, E. : Concu.

[21669] Further studies establishing the function and utilities of MYEOV are found in John Hopkins OMIM database record ID 605625, and in cited publications numbered 6958–6959 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Platelet–derived Growth Factor Receptor, Beta Polypeptide (PDGFRB, Accession XM\_038350) is another VGAM471 host target gene. PDGFRB BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PDGFRB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDGFRB BINDING SITE, designated SEQ ID:32812, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA,

also designated SEQ ID:3182.

[21670] Another function of VGAM471 is therefore inhibition of Platelet-derived Growth Factor Receptor, Beta Polypeptide (PDGFRB, Accession XM\_038350), a gene which Platelet-derived growth factor receptor beta chain; tyrosine kinase receptor. Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDGFRB. The function of PDGFRB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM125.Sulfotransferase Family, Cytosolic, 1C, Member 1 (SULT1C1, Accession NM\_001056) is another VGAM471 host target gene. SULT1C1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SULT1C1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SULT1C1 BINDING SITE, designated SEQ ID:6719, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21671] Another function of VGAM471 is therefore inhibition of

Sulfotransferase Family, Cytosolic, 1C, Member 1

(SULT1C1, Accession NM\_001056). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SULT1C1. DKFZP566B183 (Accession NM\_015509) is another VGAM471 host target gene. DKFZP566B183 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP566B183, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566B183 BINDING SITE, designated SEQ ID:17767, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21672] Another function of VGAM471 is therefore inhibition of DKFZP566B183 (Accession NM\_015509). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566B183. DNAM-1 (Accession NM\_006566) is another VGAM471 host target gene. DNAM-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DNAM-1, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNAM-1 BINDING SITE, designated SEQ ID:13336, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21673] Another function of VGAM471 is therefore inhibition of DNAM-1 (Accession NM\_006566). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNAM-1. FLJ10751 (Accession NM\_018205) is another VGAM471 host target gene. FLJ10751 BINDING SITE1 and FLJ10751 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ10751, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10751 BINDING SITE1 and FLJ10751 BINDING SITE2, designated SEQ ID:20093 and SEQ ID:20192 respectively, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21674] Another function of VGAM471 is therefore inhibition of FLJ10751 (Accession NM\_018205). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ10751. KIAA1538 (Accession XM\_049474) is another VGAM471 host target gene. KIAA1538 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1538 BINDING SITE, designated SEQ ID:35429, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21675] Another function of VGAM471 is therefore inhibition of KIAA1538 (Accession XM\_049474). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1538. LEC3 (Accession NM\_015236) is another VGAM471 host target gene. LEC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LEC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LEC3 BINDING SITE, designated SEQ ID:17565, to the nucleotide sequence of

VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21676] Another function of VGAM471 is therefore inhibition of LEC3 (Accession NM\_015236). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LEC3. SNRK (Accession NM\_017719) is another VGAM471 host target gene. SNRK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SNRK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNRK BINDING SITE, designated SEQ ID:19307, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21677] Another function of VGAM471 is therefore inhibition of SNRK (Accession NM\_017719). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNRK. LOC151195 (Accession XM\_087125) is another VGAM471 host target gene. LOC151195 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of

mRNA encoded by LOC151195, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151195 BINDING SITE, designated SEQ ID:39075, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21678] Another function of VGAM471 is therefore inhibition of LOC151195 (Accession XM\_087125). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151195. LOC201952 (Accession XM\_117345) is another VGAM471 host target gene. LOC201952 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC201952, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201952 BINDING SITE, designated SEQ ID:43395, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21679] Another function of VGAM471 is therefore inhibition of LOC201952 (Accession XM\_117345). Accordingly, utilities

of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201952. LOC222183 (Accession XM\_168436) is another VGAM471 host target gene. LOC222183 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222183, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222183 BINDING SITE, designated SEQ ID:45186, to the nucleotide sequence of VGAM471 RNA, herein designated VGAM RNA, also designated SEQ ID:3182.

[21680] Another function of VGAM471 is therefore inhibition of LOC222183 (Accession XM\_168436). Accordingly, utilities of VGAM471 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222183. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 472 (VGAM472) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.



[21681] VGAM472 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM472 was detected is described hereinabove with reference to Figs. 1–8.

[21682] VGAM472 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tick–borne Encephalitis Virus. VGAM472 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21683] VGAM472 gene encodes a VGAM472 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM472 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM472 precursor RNA is designated SEQ ID:458, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:458 is located at position 8516 relative to the genome of Tick–borne Encephalitis Virus.

[21684] VGAM472 precursor RNA folds onto itself, forming VGAM472 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two–dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21685] An enzyme complex designated DICER COMPLEX, `dices` the VGAM472 folded precursor RNA into VGAM472 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM472 RNA is designated SEQ ID:3183, and is provided hereinbelow with reference to the sequence listing part.

[21686] VGAM472 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM472 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM472 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[21687] VGAM472 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM472 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM472 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM472 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM472 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21688] The complementary binding of VGAM472 RNA, herein designated VGAM RNA, to host target binding sites on VGAM472 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM472 host target RNA into VGAM472 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21689] It is appreciated that VGAM472 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM472 host target genes. The mRNA of each one of this plurality of VGAM472 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM472 RNA, herein designated VGAM RNA, and which when bound by VGAM472 RNA causes inhibition of translation of respective one or more VGAM472 host target proteins.

[21690] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM472 gene, herein designated VGAM GENE, on one or more VGAM472 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21691] It is yet further appreciated that a function of VGAM472 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of viral infection by Tick-borne Encephalitis Virus. Specific functions, and accordingly utilities, of VGAM472 correlate with, and may be deduced from, the identity of the host target genes which VGAM472 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21692] Nucleotide sequences of the VGAM472 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM472 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM472 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM472 are further  
described hereinbelow with reference to Table 1.

[21693] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM472 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM472 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[21694] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM472 gene, herein designated VGAM is  
inhibition of expression of VGAM472 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM472 correlate with, and may be deduced  
from, the identity of the target genes which VGAM472  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[21695] F-box Only Protein 9 (FBXO9, Accession NM\_033481) is a  
VGAM472 host target gene. FBXO9 BINDING SITE is HOST

TARGET binding site found in the 5` untranslated region of mRNA encoded by FBXO9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO9 BINDING SITE, designated SEQ ID:27260, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21696] A function of VGAM472 is therefore inhibition of F-box Only Protein 9 (FBXO9, Accession NM\_033481). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXO9. FLJ14950 (Accession NM\_032865) is another VGAM472 host target gene. FLJ14950 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14950, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14950 BINDING SITE, designated SEQ ID:26674, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21697] Another function of VGAM472 is therefore inhibition of

FLJ14950 (Accession NM\_032865). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14950. FLJ22362 (Accession NM\_022823) is another VGAM472 host target gene. FLJ22362 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ22362, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22362 BINDING SITE, designated SEQ ID:23103, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21698] Another function of VGAM472 is therefore inhibition of FLJ22362 (Accession NM\_022823). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22362. KIAA0427 (Accession NM\_014772) is another VGAM472 host target gene. KIAA0427 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0427, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of KIAA0427 BINDING SITE, designated SEQ ID:16578, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21699] Another function of VGAM472 is therefore inhibition of KIAA0427 (Accession NM\_014772). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0427. KIAA0478 (Accession NM\_014870) is another VGAM472 host target gene. KIAA0478 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0478, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0478 BINDING SITE, designated SEQ ID:16981, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21700] Another function of VGAM472 is therefore inhibition of KIAA0478 (Accession NM\_014870). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0478. KIAA1530 (Accession XM\_042661) is another

VGAM472 host target gene. KIAA1530 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1530, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1530 BINDING SITE, designated SEQ ID:33730, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21701] Another function of VGAM472 is therefore inhibition of KIAA1530 (Accession XM\_042661). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1530. LOC145676 (Accession XM\_085202) is another VGAM472 host target gene. LOC145676 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145676, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145676 BINDING SITE, designated SEQ ID:37921, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21702] Another function of VGAM472 is therefore inhibition of LOC145676 (Accession XM\_085202). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145676. LOC220575 (Accession XM\_083991) is another VGAM472 host target gene. LOC220575 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220575, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220575 BINDING SITE, designated SEQ ID:37527, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21703] Another function of VGAM472 is therefore inhibition of LOC220575 (Accession XM\_083991). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220575. LOC91547 (Accession XM\_039093) is another VGAM472 host target gene. LOC91547 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91547, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91547 BINDING SITE, designated SEQ ID:33002, to the nucleotide sequence of VGAM472 RNA, herein designated VGAM RNA, also designated SEQ ID:3183.

[21704] Another function of VGAM472 is therefore inhibition of LOC91547 (Accession XM\_039093). Accordingly, utilities of VGAM472 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91547. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 473 (VGAM473) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21705] VGAM473 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM473 was detected is described hereinabove with reference to Figs. 1–8.

[21706] VGAM473 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tick-borne Encephalitis Virus. VGAM473 host target gene, herein designated

VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21707] VGAM473 gene encodes a VGAM473 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM473 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM473 precursor RNA is designated SEQ ID:459, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:459 is located at position 9825 relative to the genome of Tick-borne Encephalitis Virus.

[21708] VGAM473 precursor RNA folds onto itself, forming VGAM473 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21709] An enzyme complex designated DICER COMPLEX, `dices` the VGAM473 folded precursor RNA into VGAM473 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM473 RNA is designated SEQ ID:3184, and is provided hereinbelow with reference to the sequence listing part.

[21710] VGAM473 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM473 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM473 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21711] VGAM473 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM473 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM473 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM473 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM473 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21712] The complementary binding of VGAM473 RNA, herein designated VGAM RNA, to host target binding sites on VGAM473 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM473 host target RNA into VGAM473 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[21713] It is appreciated that VGAM473 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM473 host target genes. The mRNA of each one of this plurality of VGAM473 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM473 RNA, herein designated VGAM RNA, and which when bound by VGAM473 RNA causes inhibition of translation of respective one or more VGAM473 host target proteins.

[21714] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM473 gene, herein designated VGAM GENE, on one or more VGAM473 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-



pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21715] It is yet further appreciated that a function of VGAM473 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM473 include diagnosis, prevention and treatment of viral infection by Tick-borne Encephalitis Virus. Specific functions, and accordingly utilities, of VGAM473 correlate with, and may be deduced from, the identity of the host target genes which VGAM473 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21716] Nucleotide sequences of the VGAM473 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM473 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM473 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM473 are further described hereinbelow with reference to Table 1.

[21717] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM473 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM473 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21718] As mentioned hereinabove with reference to Fig. 1, a function of VGAM473 gene, herein designated VGAM is inhibition of expression of VGAM473 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM473 correlate with, and may be deduced from, the identity of the target genes which VGAM473 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21719] Dopamine Receptor D1 (DRD1, Accession NM\_000794) is a VGAM473 host target gene. DRD1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DRD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRD1 BINDING SITE, designated SEQ ID:6465, to the nucleotide sequence of VGAM473 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3184.

[21720] A function of VGAM473 is therefore inhibition of Dopamine Receptor D1 (DRD1, Accession NM\_000794), a gene which is mediated by g proteins which activate adenylyl cyclase. Accordingly, utilities of VGAM473 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRD1. The function of DRD1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM22.Coagulation Factor II (thrombin) Receptor (F2R, Accession NM\_001992) is another VGAM473 host target gene. F2R BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by F2R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F2R BINDING SITE, designated SEQ ID:7719, to the nucleotide sequence of VGAM473 RNA, herein designated VGAM RNA, also designated SEQ ID:3184.

[21721] Another function of VGAM473 is therefore inhibition of Coagulation Factor II (thrombin) Receptor (F2R, Accession NM\_001992), a gene which Thrombin receptor; G protein-

coupled receptor involved in platelet activation. Accordingly, utilities of VGAM473 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F2R. The function of F2R and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM140. Angiotensin II Receptor-like 2 (AGTRL2, Accession NM\_005162) is another VGAM473 host target gene. AGTRL2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by AGTRL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AGTRL2 BINDING SITE, designated SEQ ID:11646, to the nucleotide sequence of VGAM473 RNA, herein designated VGAM RNA, also designated SEQ ID:3184.

[21722] Another function of VGAM473 is therefore inhibition of Angiotensin II Receptor-like 2 (AGTRL2, Accession NM\_005162). Accordingly, utilities of VGAM473 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AGTRL2. FLJ10540 (Accession NM\_018131) is another VGAM473 host target

gene. FLJ10540 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10540, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10540 BINDING SITE, designated SEQ ID:19928, to the nucleotide sequence of VGAM473 RNA, herein designated VGAM RNA, also designated SEQ ID:3184.

[21723] Another function of VGAM473 is therefore inhibition of FLJ10540 (Accession NM\_018131). Accordingly, utilities of VGAM473 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10540. FLJ13852 (Accession NM\_023078) is another VGAM473 host target gene. FLJ13852 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13852, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13852 BINDING SITE, designated SEQ ID:23341, to the nucleotide sequence of VGAM473 RNA, herein designated VGAM RNA, also designated SEQ ID:3184.

- [21724] Another function of VGAM473 is therefore inhibition of FLJ13852 (Accession NM\_023078). Accordingly, utilities of VGAM473 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13852. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 474 (VGAM474) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [21725] VGAM474 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM474 was detected is described hereinabove with reference to Figs. 1–8.
- [21726] VGAM474 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tick-borne Encephalitis Virus. VGAM474 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.
- [21727] VGAM474 gene encodes a VGAM474 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM474 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM474 precursor RNA is designated SEQ ID:460, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:460 is located at position 7427 relative to the genome of Tick-borne Encephalitis Virus.

[21728] VGAM474 precursor RNA folds onto itself, forming VGAM474 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21729] An enzyme complex designated DICER COMPLEX, `dices` the VGAM474 folded precursor RNA into VGAM474 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide se-

quence of VGAM474 RNA is designated SEQ ID:3185, and is provided hereinbelow with reference to the sequence listing part.

[21730] VGAM474 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM474 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM474 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[21731] VGAM474 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM474 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM474 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is



meant as an illustration only, and is not meant to be limiting – VGAM474 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM474 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[21732] The complementary binding of VGAM474 RNA, herein designated VGAM RNA, to host target binding sites on VGAM474 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM474 host target RNA into VGAM474 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21733] It is appreciated that VGAM474 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM474 host target genes. The mRNA of each one of this plurality of VGAM474 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM474 RNA, herein designated VGAM RNA, and which when bound by VGAM474 RNA causes inhibition of translation of respective one or more VGAM474 host target proteins.

[21734] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM474 gene, herein designated VGAM GENE, on one or more VGAM474 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21735] It is yet further appreciated that a function of VGAM474 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of viral infection by Tick-borne Encephalitis Virus. Specific functions, and accordingly utilities, of VGAM474 correlate with, and may be deduced from, the identity of the host target genes which VGAM474 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21736] Nucleotide sequences of the VGAM474 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM474 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM474 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM474 are further described hereinbelow with reference to Table 1.

[21737] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM474 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM474 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21738] As mentioned hereinabove with reference to Fig. 1, a function of VGAM474 gene, herein designated VGAM is inhibition of expression of VGAM474 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM474 correlate with, and may be deduced from, the identity of the target genes which VGAM474 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21739] Adducin 1 (alpha) (ADD1, Accession NM\_014190) is a VGAM474 host target gene. ADD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADD1 BINDING SITE, designated SEQ ID:15471, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21740] A function of VGAM474 is therefore inhibition of Adducin 1 (alpha) (ADD1, Accession NM\_014190), a gene which membrane-cytoskeleton- protein that promotes the assembly of the spectrin-actin network. Accordingly, utilities of VGAM474 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with ADD1. The function of ADD1 has been established by previous studies. Adducin is a cell-membrane skeletal protein that was first purified from human erythrocytes by Gardner and Bennett (1986) and subsequently isolated from bovine brain membranes. Isoforms of this protein have been detected in lung, kidney, testes, and liver. Erythrocyte adducin is a 200-kD heterodimer protein present at about 30,000 copies per cell. It binds with high affinity to  $\text{Ca}^{2+}$ /calmodulin and is a substrate for protein kinases A and C. Joshi and Bennett (1990) investigated the structure and function of the separate domains of the protein. Adducin is a heterodimeric protein. The related subunits, alpha and beta (ADD2; 102681), are produced from distinct genes but share a similar structure, with a protease-resistant N-terminal region and a protease-sensitive, hydrophilic C-terminal region. Joshi et al. (1991) isolated reticulocyte cDNAs for alpha- and beta-adducin and, by somatic cell hybrid analysis, provisionally assigned the ADD1 gene to chromosome 4 and the ADD2 gene to chromosome 2. Both alpha-adducin and beta-adducin show alternative splicing; thus, there may be several different heterodimeric or homodimeric forms of adducin, each

with a different functional specificity. Adducin was thought to promote assembly of spectrin-actin complexes in the formation of the membrane cytoskeleton (the name comes from the Latin adducere, meaning 'to bring together'). At least in brain, alpha-adducin is encoded by alternatively spliced mRNAs. See Gilligan and Bennett (1993) for a review of adducin and the other components of the junctional complex of the cell membrane skeleton. Casari et al. (1995) found in humans an association between essential hypertension (see OMIM Ref. No. 145500) and some allelic markers close to the alpha-adducin locus. Cusi et al. (1997) found significant linkage of the alpha-adducin locus to essential hypertension and greater sensitivity to changes in sodium balance among patients with a particular ADD1 allele, trp460 (102680.0001), suggesting that alpha-adducin is associated with a salt-sensitive form of essential hypertension. They suggested that this polymorphism may identify hypertensive patients who will benefit from diuretic treatment or maneuvers to reduce total body sodium. Heterozygous hypertensive patients (gly/trp) showed a greater fall in mean arterial pressure in response to 2 months' treatment with hydrochlorothiazide than did wildtype homozygous (gly/gly) hypertensive pa-

tients.

[21741] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21742] Joshi, R.; Gilligan, D. M.; Otto, E.; McLaughlin, T.; Bennett, V. : Primary structure and domain organization of human alpha and beta adducin. J. Cell Biol. 115: 665–675, 1991. ; and

[21743] Cusi, D.; Barlassina, C.; Azzani, T.; Casari, G.; Citterio, L.; Devoto, M.; Glorioso, N.; Lanzani, C.; Manunta, P.; Righetti, M.; Rivera, R.; Stella, P.; Troffa, C.; Zagato, L.; Bianchi.

[21744] Further studies establishing the function and utilities of ADD1 are found in John Hopkins OMIM database record ID 102680, and in cited publications numbered 791, 3622, 3784–793, 2667, 2791, 2036–79 and 482–484 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Huntingtin Interacting Protein 1 (HIP1, Accession NM\_005338) is another VGAM474 host target gene. HIP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HIP1 BINDING SITE, designated SEQ ID:11812, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21745] Another function of VGAM474 is therefore inhibition of Huntingtin Interacting Protein 1 (HIP1, Accession NM\_005338), a gene which is a membrane protein and interacts with huntingtin. Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HIP1. The function of HIP1 has been established by previous studies. Huntington disease (HD; 143100) may be due to a toxic gain-of-function caused by abnormal protein-protein interactions related to the elongated polyglutamine sequence of huntingtin. Thus, the binding of distinct proteins to the polyglutamine region could either confer a new property on huntingtin or alter its normal interactions with other proteins. Wanker et al. (1997) hypothesized that the specific binding of a protein with a restricted pattern of expression to the elongated polyglutamine stretch of the huntingtin protein could cause selective vulnerability to particular cells. The potential huntingtin-interacting pro-



teins that have been identified include huntingtin-associated protein-1 (OMIM Ref. No. 600947), the glycolytic enzyme GAPD (OMIM Ref. No. 138400), and the ubiquitin-conjugating enzyme E2-25K, also named HIP2 (OMIM Ref. No. 602846), which binds selectively to the N terminus of huntingtin. Wanker et al. (1997) demonstrated the specific binding of a protein to the N terminus of huntingtin, both in the yeast 2-hybrid screen and in in vitro binding experiments. A protein region downstream of the polyglutamine stretch in huntingtin was essential for the interaction in vitro. Thus, the authors designated the new protein 'huntingtin-interacting protein-1' (HIP1). The HIP1 cDNA isolated by the 2-hybrid screen encodes a 55-kD fragment of the novel protein. Using an affinity-purified polyclonal antibody raised against recombinant HIP1, a protein of 116 kD was detected in brain extracts by Western blot analysis. The predicted amino acid sequence of the HIP1 fragment exhibited significant similarity to cytoskeleton proteins, suggesting to Wanker et al. (1997) that HIP1 and huntingtin play a functional role in the cell filament network. The HIP1 gene was found to be ubiquitously expressed at low levels in different brain regions. HIP1 is enriched in human brain but can also be detected in other

human tissues, as well as in mouse brain. The authors noted that HIP1 and huntingtin behave almost identically during subcellular fractionation and both proteins are enriched in the membrane-containing fractions. Animal model experiments lend further support to the function of HIP1. Kalchman et al. (1997) showed that HIP1 is a membrane-associated protein that colocalizes with huntingtin and shares sequence homology and biochemical characteristics with Sla2p, a protein essential for function of the cytoskeleton in *S. cerevisiae*. The huntingtin-HIP1 interaction was restricted to the brain and correlated inversely with the polyglutamine length in huntingtin. Their results provided a molecular link between huntingtin and the neuronal cytoskeleton and suggested that, in Huntington disease, loss of normal huntingtin-HIP1 interaction may contribute to a defect in membrane-cytoskeletal integrity in the brain.

[21746] It is appreciated that the abovementioned animal model for HIP1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21747] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [21748] Kalchman, M. A.; Koide, H. B.; McCutcheon, K.; Graham, R. K.; Nichol, K.; Nishiyama, K.; Kazemi-Esfarjani, P.; Lynn, F. C.; Wellington, C.; Metzler, M.; Goldberg, Y. P.; Kanazawa, I.; Gietz, R. D.; Hayden, M. R. : HIP1, a human homologue of *S. cerevisiae* Slap2, interacts with membrane-associated huntingtin in the brain. *Nature Genet.* 16: 44–53, 1997. ; and
- [21749] Wanker, E. E.; Rovira, C.; Scherzinger, E.; Hasenbank, R.; Walter, S.; Tait, D.; Colicelli, J.; Lehrach, H. : HIP-I: a huntingtin interacting protein isolated by the yeast two-hybrid sys.
- [21750] Further studies establishing the function and utilities of HIP1 are found in John Hopkins OMIM database record ID 601767, and in cited publications numbered 7175, 11274–2866, 672 and 9966 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Homeo Box C13 (HOXC13, Accession XM\_006804) is another VGAM474 host target gene. HOXC13 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HOXC13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of HOXC13 BINDING SITE, designated SEQ ID:30014, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21751] Another function of VGAM474 is therefore inhibition of Homeo Box C13 (HOXC13, Accession XM\_006804). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HOXC13. Jerky Homolog (mouse) (JRK, Accession XM\_098818) is another VGAM474 host target gene. JRK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JRK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JRK BINDING SITE, designated SEQ ID:41841, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21752] Another function of VGAM474 is therefore inhibition of Jerky Homolog (mouse) (JRK, Accession XM\_098818), a gene which might function as a DNA-binding protein. Accordingly, utilities of VGAM474 include diagnosis, preven-

tion and treatment of diseases and clinical conditions associated with JRK. The function of JRK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM210. Kelch-like 3 (*Drosophila*) (KLHL3, Accession XM\_113450) is another VGAM474 host target gene. KLHL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KLHL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KLHL3 BINDING SITE, designated SEQ ID:42269, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21753] Another function of VGAM474 is therefore inhibition of Kelch-like 3 (*Drosophila*) (KLHL3, Accession XM\_113450). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KLHL3. Microtubule-associated Protein 1A (MAP1A, Accession NM\_002373) is another VGAM474 host target gene. MAP1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA en-

coded by MAP1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP1A BINDING SITE, designated SEQ ID:8186, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21754] Another function of VGAM474 is therefore inhibition of Microtubule-associated Protein 1A (MAP1A, Accession NM\_002373), a gene which is a structural protein involved in the filamentous cross-bridging between microtubules and other skeletal elements. Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP1A. The function of MAP1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM315. Neuralized-like (Drosophila) (NEURL, Accession NM\_004210) is another VGAM474 host target gene. NEURL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEURL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2

illustrates the complementarity of the nucleotide sequences of NEURL BINDING SITE, designated SEQ ID:10415, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21755] Another function of VGAM474 is therefore inhibition of Neuralized-like (Drosophila) (NEURL, Accession NM\_004210). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEURL. Ovo-like 1(Drosophila) (OVOL1, Accession NM\_004561) is another VGAM474 host target gene. OVOL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OVOL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OVOL1 BINDING SITE, designated SEQ ID:10900, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21756] Another function of VGAM474 is therefore inhibition of Ovo-like 1(Drosophila) (OVOL1, Accession NM\_004561). Accordingly, utilities of VGAM474 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with OVOL1. UDP Glycosyltransferase 1 Family, Polypeptide A1 (UGT1A1, Accession NM\_000463) is another VGAM474 host target gene. UGT1A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UGT1A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UGT1A1 BINDING SITE, designated SEQ ID:6082, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21757] Another function of VGAM474 is therefore inhibition of UDP Glycosyltransferase 1 Family, Polypeptide A1 (UGT1A1, Accession NM\_000463). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UGT1A1. UDP Glycosyltransferase 1 Family, Polypeptide A4 (UGT1A4, Accession NM\_007120) is another VGAM474 host target gene. UGT1A4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UGT1A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or



BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UGT1A4 BINDING SITE, designated SEQ ID:13980, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21758] Another function of VGAM474 is therefore inhibition of UDP Glycosyltransferase 1 Family, Polypeptide A4 (UGT1A4, Accession NM\_007120), a gene which is of major importance in the conjugation and subsequent elimination of potentially toxic xenobiotics and endogenous compounds. Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UGT1A4. The function of UGT1A4 has been established by previous studies. By screening a liver cDNA library with a probe to a conserved transferase C-terminal sequence, followed by 5-prime RACE, Ritter et al. (1991) obtained cDNAs encoding UGT1A1 and UGT1A4, which they termed HUGBR1 and HUGBR2, respectively. The deduced 534-amino acid UGT1A4 protein shares 66% sequence similarity with UGT1A1 in the N terminus, which contains potential N-linked glycosylation sites, and complete identity after codon 287. Northern blot analysis revealed expression of

a 2.6-kb transcript in liver. Unlike UGT1A1, expression of UGT1A4 is normal in type I Crigler–Najjar syndrome (OMIM Ref. No. 218800). Functional analysis showed that UGT1A4 has glucuronidating activity although, in a review of the UGTs, Tukey and Strassburg (2000) found that UGT1A4 activity with bilirubin is rather modest compared to that of UGT1A1. UGT1A4 is relatively active with amines, steroids, and sapogenins. By Northern blot analysis, Ritter et al. (1992) determined that UGT1A4, then termed UGT1D, is expressed at lower levels than UGT1A1 in liver. By Southern blot analysis, Ritter et al. (1992) determined that all of the UGT1A genes map to the same locus on chromosome 2.

[21759] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21760] Ritter, J. K.; Chen, F.; Sheen, Y. Y.; Tran, H. M.; Kimura, S.; Yeatman, M. T.; Owens, I. S. : A novel complex locus UGT1 encodes human bilirubin, phenol, and other UDP–glucuronosyltransferase isozymes with identical carboxyl termini. *J. Biol. Chem.* 267: 3257–3261, 1992. ; and

[21761] Tukey, R. H.; Strassburg, C. P. : Human UDP–glucuronosyltransferases: metabolism, expression, and

disease. Annu. Rev. Pharm. Toxicol. 40: 581–616, 2000.

[21762] Further studies establishing the function and utilities of UGT1A4 are found in John Hopkins OMIM database record ID 606429, and in cited publications numbered 1244 and 12449 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. UDP Glycosyltransferase 1 Family, Polypeptide A9 (UGT1A9, Accession NM\_021027) is another VGAM474 host target gene. UGT1A9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UGT1A9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UGT1A9 BINDING SITE, designated SEQ ID:22016, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21763] Another function of VGAM474 is therefore inhibition of UDP Glycosyltransferase 1 Family, Polypeptide A9 (UGT1A9, Accession NM\_021027), a gene which is of major importance in the conjugation and subsequent elimination of potentially toxic xenobiotics and endogenous compounds. Accordingly, utilities of VGAM474 include di-

agnosis, prevention and treatment of diseases and clinical conditions associated with UGT1A9. The function of UGT1A9 has been established by previous studies. By screening a liver cDNA library with a UGT1A6 (OMIM Ref. No. 606431) probe, Wooster et al. (1991) isolated a cDNA encoding UGT1A9, which they termed HLUGP4. The deduced 531-amino acid protein shares 67% overall sequence identity with UGT1A1 but only 38% in the N terminus. Western blot analysis showed expression of a 56-kD protein. Functional analysis indicated that, like UGT1A6, UGT1A9 is most active towards halogenated phenols with higher UGT1A9 activity with simple phenols. Findlay et al. (2000) reported that the predominant thyroid hormone released from the thyroid gland, T4, and the inactive rat T3 were glucuronidated by cloned expressed bilirubin UGT1A1 and also phenol UGT1A9. Results from Crigler-Najjar (see OMIM Ref. No. 218800) microsomal samples indicated that UGT1A1 was the main contributor to thyroid hormone glucuronidation in the liver, with rat T3 being the preferential substrate. In kidney microsomes, thyroid hormone glucuronidation was more complex, suggesting that more than just the UGT1A9 isoform may be involved. Bioactive T3 was not significantly glucuronidated

by these isoforms and other UGTs, and sulfotransferases may have been involved.

[21764] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21765] Wooster, R.; Sutherland, L.; Ebner, T.; Clarke, D.; Da Cruz e Silva, O.; Burchell, B. : Cloning and stable expression of a new member of the human liver phenol/bilirubin:UDP-glucuronosyltransferase cDNA family. *Biochem. J.* 278: 465–469, 1991. ; and

[21766] Findlay, K. A. B.; Kaptein, E.; Visser, T. J.; Burchell, B. : Characterization of the uridine diphosphate–glucuronosyltransferase–catalyzing thyroid hormone glucuronidation in man. *J. C.*

[21767] Further studies establishing the function and utilities of UGT1A9 are found in John Hopkins OMIM database record ID 606434, and in cited publications numbered 608 and 6081 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 9 Open Reading Frame 14 (C9orf14, Accession XM\_098859) is another VGAM474 host target gene. C9orf14 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by C9orf14, corre–

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C9orf14 BINDING SITE, designated SEQ ID:41910, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21768] Another function of VGAM474 is therefore inhibition of Chromosome 9 Open Reading Frame 14 (C9orf14, Accession XM\_098859). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C9orf14. CGI-01 (Accession NM\_015935) is another VGAM474 host target gene. CGI-01 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CGI-01, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CGI-01 BINDING SITE, designated SEQ ID:18056, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21769] Another function of VGAM474 is therefore inhibition of CGI-01 (Accession NM\_015935). Accordingly, utilities of

VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CGI-01. DKFZp434C0923 (Accession NM\_017598) is another VGAM474 host target gene. DKFZp434C0923 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp434C0923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434C0923 BINDING SITE, designated SEQ ID:19063, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21770] Another function of VGAM474 is therefore inhibition of DKFZp434C0923 (Accession NM\_017598). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434C0923. DnaJ (Hsp40) Homolog, Subfamily C, Member 5 (DNAJC5, Accession XM\_028966) is another VGAM474 host target gene. DNAJC5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DNAJC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNAJC5 BINDING SITE, designated SEQ ID:30811, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21771] Another function of VGAM474 is therefore inhibition of DnaJ (Hsp40) Homolog, Subfamily C, Member 5 (DNAJC5, Accession XM\_028966). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNAJC5. FLJ23584 (Accession NM\_024588) is another VGAM474 host target gene. FLJ23584 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23584, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23584 BINDING SITE, designated SEQ ID:23822, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21772] Another function of VGAM474 is therefore inhibition of FLJ23584 (Accession NM\_024588). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with FLJ23584. HYA22 (Accession NM\_005808) is another VGAM474 host target gene. HYA22 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HYA22, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HYA22 BINDING SITE, designated SEQ ID:12389, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21773] Another function of VGAM474 is therefore inhibition of HYA22 (Accession NM\_005808). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HYA22. KIAA0237 (Accession NM\_014747) is another VGAM474 host target gene. KIAA0237 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0237 BINDING SITE, designated SEQ ID:16443, to the nucleotide sequence of

VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21774] Another function of VGAM474 is therefore inhibition of KIAA0237 (Accession NM\_014747). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0237. KIAA1546 (Accession XM\_042301) is another VGAM474 host target gene. KIAA1546 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1546, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1546 BINDING SITE, designated SEQ ID:33717, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21775] Another function of VGAM474 is therefore inhibition of KIAA1546 (Accession XM\_042301). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1546. LBP-9 (Accession NM\_014553) is another VGAM474 host target gene. LBP-9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by LBP-9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LBP-9 BINDING SITE, designated SEQ ID:15881, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21776] Another function of VGAM474 is therefore inhibition of LBP-9 (Accession NM\_014553). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LBP-9. Ninjurin 2 (NINJ2, Accession NM\_016533) is another VGAM474 host target gene. NINJ2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NINJ2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NINJ2 BINDING SITE, designated SEQ ID:18602, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21777] Another function of VGAM474 is therefore inhibition of Ninjurin 2 (NINJ2, Accession NM\_016533). Accordingly,

utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NINJ2. PDZ Domain Containing 2 (PDZD2, Accession XM\_087705) is another VGAM474 host target gene.

PDZD2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PDZD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDZD2 BINDING SITE, designated SEQ ID:39396, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21778] Another function of VGAM474 is therefore inhibition of PDZ Domain Containing 2 (PDZD2, Accession XM\_087705). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDZD2. PKMYT1 (Accession NM\_004203) is another VGAM474 host target gene. PKMYT1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PKMYT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of PKMYT1 BINDING SITE, designated SEQ ID:10398, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21779] Another function of VGAM474 is therefore inhibition of PKMYT1 (Accession NM\_004203). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PKMYT1. Protein Kinase, Lysine Deficient 2 (PRKWNK2, Accession XM\_117531) is another VGAM474 host target gene. PRKWNK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKWNK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKWNK2 BINDING SITE, designated SEQ ID:43520, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21780] Another function of VGAM474 is therefore inhibition of Protein Kinase, Lysine Deficient 2 (PRKWNK2, Accession XM\_117531). Accordingly, utilities of VGAM474 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKWINK2. Sideroflexin 2 (SFXN2, Accession XM\_058359) is another VGAM474 host target gene. SFXN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFXN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFXN2 BINDING SITE, designated SEQ ID:36602, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21781] Another function of VGAM474 is therefore inhibition of Sideroflexin 2 (SFXN2, Accession XM\_058359). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFXN2. Syntaphilin (SNPH, Accession NM\_014723) is another VGAM474 host target gene. SNPH BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SNPH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

SNPH BINDING SITE, designated SEQ ID:16292, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21782] Another function of VGAM474 is therefore inhibition of Syntaphilin (SNPH, Accession NM\_014723). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNPH. LOC147599 (Accession XM\_097253) is another VGAM474 host target gene. LOC147599 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147599, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147599 BINDING SITE, designated SEQ ID:40848, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21783] Another function of VGAM474 is therefore inhibition of LOC147599 (Accession XM\_097253). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147599. LOC150383 (Accession XM\_086905) is another VGAM474 host target gene. LOC150383 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150383, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150383 BINDING SITE, designated SEQ ID:38947, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21784] Another function of VGAM474 is therefore inhibition of LOC150383 (Accession XM\_086905). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150383. LOC151836 (Accession XM\_098124) is another VGAM474 host target gene. LOC151836 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151836, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151836 BINDING SITE, designated SEQ ID:41391, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21785] Another function of VGAM474 is therefore inhibition of



LOC151836 (Accession XM\_098124). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151836. LOC221421 (Accession XM\_166428) is another VGAM474 host target gene. LOC221421 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221421, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221421 BINDING SITE, designated SEQ ID:44325, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21786] Another function of VGAM474 is therefore inhibition of LOC221421 (Accession XM\_166428). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221421. LOC255196 (Accession XM\_173157) is another VGAM474 host target gene. LOC255196 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC255196 BINDING SITE, designated SEQ ID:46415, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21787] Another function of VGAM474 is therefore inhibition of LOC255196 (Accession XM\_173157). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255196. LOC256337 (Accession XM\_170643) is another VGAM474 host target gene. LOC256337 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC256337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256337 BINDING SITE, designated SEQ ID:45422, to the nucleotide sequence of VGAM474 RNA, herein designated VGAM RNA, also designated SEQ ID:3185.

[21788] Another function of VGAM474 is therefore inhibition of LOC256337 (Accession XM\_170643). Accordingly, utilities of VGAM474 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256337. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 475 (VGAM475) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21789] VGAM475 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM475 was detected is described hereinabove with reference to Figs. 1–8.

[21790] VGAM475 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tick-borne Encephalitis Virus. VGAM475 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21791] VGAM475 gene encodes a VGAM475 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM475 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM475 precursor RNA is designated SEQ ID:461, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:461 is

located at position 606 relative to the genome of Tick-borne Encephalitis Virus.

[21792] VGAM475 precursor RNA folds onto itself, forming VGAM475 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21793] An enzyme complex designated DICER COMPLEX, `dices` the VGAM475 folded precursor RNA into VGAM475 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM475 RNA is designated SEQ ID:3186, and is provided hereinbelow with reference to the sequence listing part.

[21794] VGAM475 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM475 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM475 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[21795] VGAM475 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM475 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM475 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM475 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM475 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[21796] The complementary binding of VGAM475 RNA, herein designated VGAM RNA, to host target binding sites on VGAM475 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM475 host target RNA into VGAM475 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21797] It is appreciated that VGAM475 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM475 host target genes. The mRNA of each one of this plurality of VGAM475 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM475 RNA, herein designated VGAM RNA, and which when bound by VGAM475 RNA causes inhibition of translation of respective one or more VGAM475

host target proteins.

[21798] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM475 gene, herein designated VGAM GENE, on one or more VGAM475 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21799] It is yet further appreciated that a function of VGAM475 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of viral infection by Tick-borne Encephalitis

Virus. Specific functions, and accordingly utilities, of VGAM475 correlate with, and may be deduced from, the identity of the host target genes which VGAM475 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21800] Nucleotide sequences of the VGAM475 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM475 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM475 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM475 are further described hereinbelow with reference to Table 1.

[21801] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM475 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM475 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[21802] As mentioned hereinabove with reference to Fig. 1, a function of VGAM475 gene, herein designated VGAM is inhibition of expression of VGAM475 target genes. It is appreciated that specific functions, and accordingly utili-



ties, of VGAM475 correlate with, and may be deduced from, the identity of the target genes which VGAM475 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21803] Rac/Cdc42 Guanine Nucleotide Exchange Factor (GEF) 6 (ARHGEF6, Accession XM\_042963) is a VGAM475 host target gene. ARHGEF6 BINDING SITE1 and ARHGEF6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ARHGEF6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGEF6 BINDING SITE1 and ARHGEF6 BINDING SITE2, designated SEQ ID:33843 and SEQ ID:33850 respectively, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21804] A function of VGAM475 is therefore inhibition of Rac/Cdc42 Guanine Nucleotide Exchange Factor (GEF) 6 (ARHGEF6, Accession XM\_042963). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGEF6. Calbindin 1, 28kDa (CALB1, Accession NM\_004929) is another VGAM475 host target gene.

CALB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CALB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CALB1 BINDING SITE, designated SEQ ID:11370, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21805] Another function of VGAM475 is therefore inhibition of Calbindin 1, 28kDa (CALB1, Accession NM\_004929), a gene which buffers cytosolic calcium. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CALB1. The function of CALB1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM266. E2F Transcription Factor 3 (E2F3, Accession NM\_001949) is another VGAM475 host target gene. E2F3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by E2F3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of E2F3 BINDING SITE, designated SEQ ID:7666, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21806] Another function of VGAM475 is therefore inhibition of E2F Transcription Factor 3 (E2F3, Accession NM\_001949), a gene which binds dna and controls cell-cycle progression from g1 to s phase. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with E2F3. The function of E2F3 has been established by previous studies. MYC (OMIM Ref. No. 190080) induces transcription of the E2F1, E2F2 (OMIM Ref. No. 600426), and E2F3 genes. Using primary mouse embryo fibroblasts deleted for individual E2f genes, Leone et al. (2001) showed that MYC-induced S phase and apoptosis requires distinct E2F activities. The ability of Myc to induce S phase was impaired in the absence of either E2f2 or E2f3 but not E2f1 or E2f4 (OMIM Ref. No. 600659). In contrast, the ability of Myc to induce apoptosis was markedly reduced in cells deleted for E2f1 but not E2f2 or E2f3. The authors proposed that the induction of specific E2F activities is an essential component in the MYC pathways that control cell proliferation

and cell fate decisions. Animal model experiments lend further support to the function of E2F3. Cloud et al. (2002) generated E2f3-null mice. They found that E2f3 was essential for embryonic viability in the pure 129/Sv background, but that the presence of C57BL/6 alleles yielded some adult survivors. Although growth retarded, surviving E2f3 -/- animals were initially healthy and exhibited no obvious tumor phenotype. They died prematurely, however, with signs typical of congestive heart failure, a defect completely distinct from those reported in E2f1-null mice. Cloud et al. (2002) also generated E2f1/E2f3 compound mutant mice and found that almost all of the developmental and age-related defects arising in the individual E2f1- or E2f3-null mice were exacerbated by the mutation of the other E2f. One major difference in the properties of E2f1 and E2f3 loss was that, either alone or in combination with loss of E2f1, E2f3 mutants did not show an increase in the incidence of tumor formation.

[21807] It is appreciated that the abovementioned animal model for E2F3 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21808] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

[21809] Leone, G.; Sears, R.; Huang, E.; Rempel, R.; Nuckolls, F.; Park, C.-H.; Giangrande, P.; Wu, L.; Saavedra, H. I.; Field, S. J.; Thompson, M. A.; Yang, H.; Fujiwara, Y.; Greenberg, M. E.; Orkin, S.; Smith, C.; Nevins, J. R. : Myc requires distinct E2F activities to induce S phase and apoptosis. Molec. Cell 8: 105–113, 2001. ; and

[21810] Cloud, J. E.; Rogers, C.; Reza, T. L.; Ziebold, U.; Stone, J. R.; Picard, M. H.; Caron, A. M.; Bronson, R. T.; Lees, J. A. : Mutant mouse models reveal the relative roles of E2F1 and E2.

[21811] Further studies establishing the function and utilities of E2F3 are found in John Hopkins OMIM database record ID 600427, and in cited publications numbered 7563–7564, 756 and 9711 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Egl Nine Homolog 1 (C. elegans) (EGLN1, Accession NM\_022051) is another VGAM475 host target gene. EGLN1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by EGLN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2

illustrates the complementarity of the nucleotide sequences of EGLN1 BINDING SITE, designated SEQ ID:22580, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21812] Another function of VGAM475 is therefore inhibition of Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051), a gene which is expressed in the cytoplasm of arterial smooth muscle cells. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN1. The function of EGLN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM216. Huntingtin Interacting Protein 1 (HIP1, Accession NM\_005338) is another VGAM475 host target gene. HIP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HIP1 BINDING SITE, designated SEQ ID:11813, to the nucleotide sequence of VGAM475 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3186.

[21813] Another function of VGAM475 is therefore inhibition of Huntingtin Interacting Protein 1 (HIP1, Accession NM\_005338), a gene which is a membrane protein and interacts with huntingtin. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HIP1. The function of HIP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM474. Holocarboxylase Synthetase (biotin-[propionyl-Coenzyme A-carboxylase (ATP-hydrolysing)] Ligase) (HLCS, Accession NM\_000411) is another VGAM475 host target gene. HLCS BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HLCS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HLCS BINDING SITE, designated SEQ ID:5993, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21814] Another function of VGAM475 is therefore inhibition of

## Holocarboxylase Synthetase

(biotin-[propionyl-Coenzyme A-carboxylase

(ATP-hydrolysing)] Ligase) (HLCS, Accession NM\_000411).

Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HLCS. Interleukin 1, Alpha (IL1A, Accession XM\_031221) is another VGAM475 host target gene. IL1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL1A BINDING SITE, designated SEQ ID:31306, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21815] Another function of VGAM475 is therefore inhibition of Interleukin 1, Alpha (IL1A, Accession XM\_031221), a gene which stimulates thymocyte proliferation by inducing il-2 release, b-cell maturation & proliferation, & fibroblast growth factor activity. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL1A. The function of IL1A has been established by previous studies. There



are 2 structurally distinct forms of IL1: IL1(alpha), which is the acidic form with pI5, and IL1(beta) (IL1B; 147720), the neutral form with pI7. Both are 17-kD proteins coded by separate genes. The IL1A gene has 10,206 bp with 7 exons and 6 introns (Furutani et al., 1986). By Southern transfer analysis of DNAs from human-rodent somatic cell hybrids, Modi et al. (1988) assigned the IL1A gene to chromosome 2. Regional localization to 2q13-q21 was achieved by in situ hybridization. Lafage et al. (1989) confirmed assignment to 2q13 by in situ hybridization. The IL1A and IL1B proteins, which are synthesized by a variety of cell types including activated macrophages, keratinocytes, stimulated B lymphocytes, and fibroblasts, are potent mediators of inflammation and immunity. Lord et al. (1991) demonstrated that both the alpha and beta forms, but particularly the beta form, are transcribed in polymorphonuclear leukocytes stimulated with LPS. Both IL1A and IL1B stimulate osteoclast activity in vitro and are potent bone resorbing factors. Sabatino et al. (1988) studied the effects of 72-hour subcutaneous infusions of interleukins 1-alpha and -beta on plasma, calcium, and bone morphology. Both interleukins 1 caused a marked, dose-dependent increase in plasma calcium. Increased

numbers of osteoclasts and bone resorption surfaces were observed on quantitative histomorphometry of bone. The results suggest a role for IL1 in the modulation of extracellular fluid calcium homeostasis. Hogquist et al. (1991) demonstrated that interleukin-1 is involved in apoptosis (cell death). Both the alpha and the beta forms are released as a consequence of cell injury regardless of the insult Ki et al. (2001) analyzed the IL1A -889 C/T genotype of 126 Korean patients with AD and found no significant difference in allele frequencies between patients and controls. Interestingly, there were no T/T homozygotes in the entire study population

[21816] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21817] Hogquist, K. A.; Nett, M. A.; Unanue, E. R.; Chaplin, D. D. : Interleukin 1 is processed and released during apoptosis. Proc. Nat. Acad. Sci. 88: 8485-8489, 1991. ; and

[21818] Ki, C.-S.; Na, D. L.; Kim, D. K.; Kim, H. J.; Kim, J.-W. : Lack of association of the interleukin-1-alpha gene polymorphism with Alzheimer's disease in a Korean population. (Letter) Ann.

[21819] Further studies establishing the function and utilities of

IL1A are found in John Hopkins OMIM database record ID 147760, and in cited publications numbered 4142–4157, 4139–4141, 4158, 1116 and 11331–11334 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Mitogen-activated Protein Kinase Kinase Kinase 7 Interacting Protein 1 (MAP3K7IP1, Accession NM\_006116) is another VGAM475 host target gene. MAP3K7IP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAP3K7IP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP3K7IP1 BINDING SITE, designated SEQ ID:12763, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21820] Another function of VGAM475 is therefore inhibition of Mitogen-activated Protein Kinase Kinase Kinase 7 Interacting Protein 1 (MAP3K7IP1, Accession NM\_006116), a gene which may be an important signaling intermediate between tgfb receptors and map3k7/tak1. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with MAP3K7IP1. The function of MAP3K7IP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM132. Microtubule-associated Protein Tau (MAPT, Accession NM\_005910) is another VGAM475 host target gene. MAPT BINDING SITE1 through MAPT BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MAPT, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPT BINDING SITE1 through MAPT BINDING SITE4, designated SEQ ID:12542, SEQ ID:18830, SEQ ID:18836 and SEQ ID:18842 respectively, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21821] Another function of VGAM475 is therefore inhibition of Microtubule-associated Protein Tau (MAPT, Accession NM\_005910), a gene which Microtubule-associated protein tau; promotes microtubule assembly. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with MAPT. The function of MAPT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178. POU Domain, Class 2, Associating Factor 1 (POU2AF1, Accession NM\_006235) is another VGAM475 host target gene. POU2AF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POU2AF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POU2AF1 BINDING SITE, designated SEQ ID:12894, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21822] Another function of VGAM475 is therefore inhibition of POU Domain, Class 2, Associating Factor 1 (POU2AF1, Accession NM\_006235), a gene which is a transcriptional coactivator that specifically associates with either oct1 or oct2. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POU2AF1. The function of POU2AF1 and its association with various diseases and clinical conditions, has been established by previous studies, as de-

scribed hereinabove with reference to VGAM171.PR Domain Containing 2, with ZNF Domain (PRDM2, Accession NM\_012231) is another VGAM475 host target gene. PRDM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRDM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRDM2 BINDING SITE, designated SEQ ID:14530, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21823] Another function of VGAM475 is therefore inhibition of PR Domain Containing 2, with ZNF Domain (PRDM2, Accession NM\_012231), a gene which plays a role in transcriptional regulation during neuronal differentiation and pathogenesis of retinoblastoma. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRDM2. The function of PRDM2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM120.Secreted Frizzled-related Protein 1 (SFRP1,

Accession NM\_003012) is another VGAM475 host target gene. SFRP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SFRP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRP1 BINDING SITE, designated SEQ ID:8932, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21824] Another function of VGAM475 is therefore inhibition of Secreted Frizzled-related Protein 1 (SFRP1, Accession NM\_003012), a gene which is a receptor for wnt proteins that may have an anti-apoptotic function. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRP1. The function of SFRP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM250. Serine Hydroxymethyltransferase 1 (soluble) (SHMT1, Accession NM\_004169) is another VGAM475 host target gene. SHMT1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by SHMT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SHMT1 BINDING SITE, designated SEQ ID:10375, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21825] Another function of VGAM475 is therefore inhibition of Serine Hydroxymethyltransferase 1 (soluble) (SHMT1, Accession NM\_004169), a gene which interconverts serine and glycine. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SHMT1. The function of SHMT1 has been established by previous studies. Serine hydroxymethyltransferase (SHMT), a pyridoxal phosphate-containing enzyme, catalyzes the reversible conversion of serine and tetrahydrofolate to glycine and 5,10-methylene tetrahydrofolate. Some eukaryotic cells, including human cells, contain both cytosolic and mitochondrial forms of SHMT. Mammalian cells that lack mitochondrial SHMT activity are auxotrophic for glycine (SHMT2; 138450). It has been suggested that glycine synthesis from serine occurs in the mitochondria, whereas cytosolic SHMT may catalyze



the conversion of glycine to serine, although direct evidence for this proposal is lacking. Garrow et al. (1993) cloned human cDNAs for cytosolic and mitochondrial SHMT by functional complementation of an *Escherichia coli* glyA mutant with a human cDNA library. The cDNA for the cytosolic enzyme encoded a 483-residue protein of M(r) 53,020. The deduced protein sequence shared 63% identity with that of the SHMT2 protein. By isotopic in situ hybridization, Garrow et al. (1993) assigned the cytosolic and mitochondrial SHMT genes to 17p11.2 and 12q13, respectively. The high degree of nucleotide sequence identity between the 2 isozymes as well as the presence of keratin genes in both chromosomal regions was consistent with these regions of chromosomes 12 and 17 having arisen by a duplication event. Folate-dependent one-carbon metabolism is critical for the synthesis of numerous cellular constituents required for cell growth, and SHMT is central to this process. Elsea et al. (1995) found that the SHMT1 gene maps to the critical interval for Smith-Magenis syndrome (SMS; 182290) on 17p11.2. They found that the gene spans approximately 40 kb. It was found to be deleted in all 26 SMS patients examined by PCR, fluorescence in situ hybridization, and/or South-

ern analysis. Furthermore, haploinsufficiency was indicated by the fact that SHMT enzyme activity in patient lymphoblasts was approximately 50% that of unaffected parent lymphoblasts. They suggested that haploinsufficiency may play a role in the SMS phenotype and that this finding may point to possible therapeutic interventions.

[21826] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21827] Garrow, T. A.; Brenner, A. A.; Whitehead, V. M.; Chen, X.-N.; Duncan, R. G.; Korenberg, J. R.; Shane, B. : Cloning of human cDNAs encoding mitochondrial and cytosolic serine hydroxymethyltransferases and chromosomal localization. J. Biol. Chem. 268: 11910–11916, 1993. ; and

[21828] Elsea, S. H.; Juyal, R. C.; Jiralerspong, S.; Finucane, B. M.; Pandolfo, M.; Greenberg, F.; Baldini, A.; Stover, P.; Patel, P. I. : Haploinsufficiency of cytosolic serine hydroxymethyltran.

[21829] Further studies establishing the function and utilities of SHMT1 are found in John Hopkins OMIM database record ID 182144, and in cited publications numbered 1142–114 and 4810 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.Sorbin

and SH3 Domain Containing 1 (SORBS1, Accession NM\_015385) is another VGAM475 host target gene. SORBS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SORBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SORBS1 BINDING SITE, designated SEQ ID:17690, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21830] Another function of VGAM475 is therefore inhibition of Sorbin and SH3 Domain Containing 1 (SORBS1, Accession NM\_015385), a gene which necessary for cell polarization during vegetative growth. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORBS1. The function of SORBS1 has been established by previous studies. Lin et al. (2001) identified 14 single-nucleotide polymorphisms (SNPs) in the human SH3P12 gene, which they called SORBS1. Studies in 202 nonobese, 113 obese, and 455 subjects with type II diabetes (OMIM Ref. No. 125853) revealed that the alanine allele of a T228A poly-

morphism in exon 7 exerted a protective role for both obesity (OMIM Ref. No. 601665) (relative risk 0.466; 95% confidence interval 0.265 to 0.821) and diabetes (relative risk 0.668; 95% confidence interval 0.472 to 0.945). Neither allele of the R74W polymorphism was associated with either obesity or diabetes. The authors suggested that the SH3P12 gene may play an important role in the pathogenesis of human disorders with insulin resistance. Insulin stimulates the transport of glucose into fat and muscle cells and initiates its actions by binding to its tyrosine kinase receptor, leading to the phosphorylation of intracellular substrates. One such substrate is the CBL protooncogene product. CBL is recruited to the insulin receptor by interaction with the adaptor protein CAP, through 1 of 3 adjacent SH3 domains in the C terminus of CAP. Upon phosphorylation of CBL, the CAP-CBL complex dissociates from the insulin receptor and moves to a caveolin (see OMIM Ref. No. 601047)-enriched triton-insoluble membrane fraction (Mastick et al., 1995). To identify a molecular mechanism underlying this subcellular redistribution, Baumann et al. (2000) screened a yeast 2-hybrid library using the N-terminal region of CAP and identified the caveolar protein flotillin (OMIM Ref. No. 131560). Flotillin

forms a ternary complex with CAP and CBL, directing the localization of the CAP–CBL complex to a lipid raft subdomain of the plasma membrane. Expression of the N-terminal domain of CAP in 3T3–L1 adipocytes blocks the stimulation of glucose transport by insulin, without affecting signaling events that depend on phosphatidylinositol–3–OH kinase (see OMIM Ref. No. 602838). Thus, localization of the CBL–CAP complex to lipid rafts generates a pathway that is crucial in the regulation of glucose uptake.

[21831] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21832] Lin, W.–H.; Chiu, K. C.; Chang, H.–M.; Lee, K.–C.; Tai, T.–Y.; Chuang, L.–M. : Molecular scanning of the human sorbin and SH3–domain–containing–1 (SORBS1) gene: positive association of the T228A polymorphism with obesity and type 2 diabetes. *Hum. Molec. Genet.* 10: 1753–1760, 2001. ; and

[21833] Baumann, C. A.; Ribon, V.; Kanzaki, M.; Thurmond, D. C.; Mora, S.; Shigematsu, S.; Bickel, P. E.; Pessin, J. E.; Saltiel, A. R. : CAP defines a second signalling pathway required for insulin.

[21834] Further studies establishing the function and utilities of SORBS1 are found in John Hopkins OMIM database record ID 605264, and in cited publications numbered 4598, 11935–5034, 1090 and 11936 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. **Sepiapterin Reductase** (7,8–dihydrobiopterin:NADP+ oxidoreductase) (SPR, Accession NM\_003124) is another VGAM475 host target gene. SPR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPR BINDING SITE, designated SEQ ID:9094, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21835] Another function of VGAM475 is therefore inhibition of Sepiapterin Reductase (7,8–dihydrobiopterin:NADP+ oxidoreductase) (SPR, Accession NM\_003124), a gene which catalyzes the. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPR. The function of SPR has been established by previous studies. Bonafe et al.

(2001) reported 2 patients with progressive psychomotor retardation, dystonia, severe dopamine and serotonin deficiencies (low levels of 5-hydroxyindoleacetic and homovanillic acids), and abnormal pterin pattern (high levels of biopterin and dihydrobiopterin) in cerebrospinal fluid. They presented with normal urinary pterins and without hyperphenylalaninemia. Studies of skin fibroblasts revealed inactive sepiapterin reductase, the enzyme catalyzing the final 2-step reaction in the biosynthesis of tetrahydrobiopterin (BH4). Mutations in the SPR gene were detected in both patients: homozygous (182125.0001) in 1 and compound heterozygous (182125.0002) in the other. The authors suggested that autosomal recessive deficiency of sepiapterin reductase leads to BH4 and neurotransmitter deficiencies without hyperphenylalaninemia and may not be detected by neonatal screening for phenylketonuria.

[21836] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21837] Bonafe, L.; Thony, B.; Penzien, J. M.; Czarnecki, B.; Blau, N. : Mutations in the sepiapterin reductase gene cause a novel tetrahydrobiopterin-dependent monoamine-

neurotransmitter deficiency without hyperphenylalaninemia. Am. J. Hum. Genet. 69: 269–277, 2001. ; and

[21838] Blau, N.; Thony, B.; Renneberg, A.; Arnold, L. A.; Hyland, K. : Dihydropteridine reductase deficiency localized to the central nervous system. J. Inherit. Metab. Dis. 21: 433–434, 1998.

[21839] Further studies establishing the function and utilities of SPR are found in John Hopkins OMIM database record ID 182125, and in cited publications numbered 10607–10612 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Topoisomerase (DNA) I (TOP1, Accession NM\_003286) is another VGAM475 host target gene. TOP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TOP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOP1 BINDING SITE, designated SEQ ID:9296, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21840] Another function of VGAM475 is therefore inhibition of Topoisomerase (DNA) I (TOP1, Accession NM\_003286).



Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOP1. Thiamin Pyrophosphokinase 1 (TPK1, Accession NM\_022445) is another VGAM475 host target gene. TPK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TPK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TPK1 BINDING SITE, designated SEQ ID:22779, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21841] Another function of VGAM475 is therefore inhibition of Thiamin Pyrophosphokinase 1 (TPK1, Accession NM\_022445), a gene which catalyzes the conversion of thiamine, a form of vitamin B1, to thiamine pyrophosphate . Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TPK1. The function of TPK1 has been established by previous studies. By Northern blot analysis, Nosaka et al. (1999) detected expression of mouse Tpk1 predominantly in kidney and liver, with very

faint expression in heart, brain, and testis. In contrast to the tissue-specific expression of mouse Tpk1, Nosaka et al. (2001) reported broad expression of a human 2.5-kb TPK1 transcript. They detected very low expression in a variety of human tissues and relatively abundant expression in heart, kidney, and peripheral leukocytes. By Northern blot analysis, Zhao et al. (2001) detected broad expression of a 2.6-kb TPK1 transcript, with highest levels in testis and in those tissues involved in thiamine absorption (small intestine) and reabsorption (OMIM Ref. No. kidney). They also detected a smaller (1–1.5 kb), testis-specific TPK1 transcript. From results of cell culture experiments, Nosaka et al. (1999) and Nosaka et al. (2001) concluded that thiamine or a thiamine derivative does not participate in the regulation of TPK1. Nosaka et al. (2001) detected no difference in TPK1 expression in cultured fibroblasts from normal subjects or from patients with thiamine-responsive megaloblastic anemia (OMIM Ref. No. 249270).

[21842] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21843] Zhao, R.; Gao, F.; Goldman, I. D. : Molecular cloning of

human thiamin pyrophosphokinase. Biochim. Biophys.

Acta 1517: 320–322, 2001. ; and

[21844] Nosaka, K.; Onozuka, M.; Nishino, H.; Nishimura, H.; Kawasaki, Y.; Ueyama, H. : Molecular cloning and expression of a mouse thiamin pyrophosphokinase cDNA. J. Biol. Chem. 274: 34129–3413.

[21845] Further studies establishing the function and utilities of TPK1 are found in John Hopkins OMIM database record ID 606370, and in cited publications numbered 6176–6178 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Wolf–Hirschhorn Syndrome Candidate 1–like 1 (WHSC1L1, Accession NM\_017778) is another VGAM475 host target gene. WHSC1L1 BINDING SITE1 and WHSC1L1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by WHSC1L1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WHSC1L1 BINDING SITE1 and WHSC1L1 BINDING SITE2, designated SEQ ID:19409 and SEQ ID:23316 respectively, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21846] Another function of VGAM475 is therefore inhibition of Wolf–Hirschhorn Syndrome Candidate 1–like 1 (WHSC1L1, Accession NM\_017778), a gene which restores repair of base–base and single– nucleotide insertion–deletion mismatches, and increases the proficiency to process heteroduplexes with insertion–deletion mismatches. Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WHSC1L1. The function of WHSC1L1 has been established by previous studies. By EST database searching with mouse Nsd1 (OMIM Ref. No. 606681) and human NSD2 (WHSC1; 602952) as probe and screening of an amnion cell cDNA library, Angrand et al. (2001) cloned a partial sequence for WHSC1L1, which they called NSD3. They obtained the full–length cDNA by 5–prime RACE. The deduced 1,437–amino acid protein contains 2 PWWP domains involved in protein–protein interaction, 5 PHD–type zinc finger motifs found in chromatin–associated proteins, a SAC (SET–associated cys–rich) domain, a SET domain, and a C–terminal C5HCH domain. They also identified a variant, arising from alternative polyadenylation and exon splicing, that encodes a deduced 645–amino acid peptide. The short isoform contains a single PWWP domain. By PCR

analysis, Angrand et al. (2001) found the 2 variants, as well as a third, 1,388–amino acid peptide, in HeLa cells. WHSC1L1 shares 68% and 55% identity with mouse Nsd1 (OMIM Ref. No. 606681) and human WHSC1 (OMIM Ref. No. 602952), respectively, over a 700–amino acid block containing the SAC, SET, and C5HCH domains. Northern blot analysis detected an 8.5–kb transcript in all tissues examined, with highest expression in brain, heart, and skeletal muscle, and lower expression in liver and lung. Angrand et al. (2001) determined that the WHSC1L1 gene contains 24 exons and spans over 90 kb. By FISH, Angrand et al. (2001) mapped the WHSC1L1 gene to chromosome 8p12. Stec et al. (2001) identified a pseudogene (WHSC1L2P) on chromosome 17q21. Rosati et al. (2002) described fusion between the NUP98 gene (OMIM Ref. No. 601021) and the NSD3 gene in a patient with acute myeloid leukemia associated with t(8;11)(p11.2;p15). FISH analysis revealed a split of a specific BAC which showed the fusion partner at 8p11.2 to be NSD3.

[21847] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21848] Angrand, P.–O.; Apiou, F.; Stewart, A. F.; Dutrillaux, B.;

Losson, R.; Chambon, P. : NSD3, a new SET domain-containing gene, maps to 8p12 and is amplified in human breast cancer cell lines. Genomics 74: 79–88, 2001. ; and

[21849] Rosati, R.; La Starza, R.; Veronese, A.; Aventin, A.; Schwienbacher, C.; Vallespi, T.; Negrini, M.; Martelli, M. F.; Mecucci, C. : NUP98 is fused to the NSD3 gene in acute myeloid leuke.

[21850] Further studies establishing the function and utilities of WHSC1L1 are found in John Hopkins OMIM database record ID 607083, and in cited publications numbered 549 and 9652 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 20 Open Reading Frame 4 (C20orf4, Accession NM\_015511) is another VGAM475 host target gene. C20orf4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf4 BINDING SITE, designated SEQ ID:17772, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21851] Another function of VGAM475 is therefore inhibition of Chromosome 20 Open Reading Frame 4 (C20orf4, Accession NM\_015511). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf4. Calcium/calmodulin-dependent Protein Kinase Kinase 2, Beta (CAMKK2, Accession NM\_006549) is another VGAM475 host target gene. CAMKK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAMKK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAMKK2 BINDING SITE, designated SEQ ID:13309, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21852] Another function of VGAM475 is therefore inhibition of Calcium/calmodulin-dependent Protein Kinase Kinase 2, Beta (CAMKK2, Accession NM\_006549). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAMKK2. CTAGE-1 (Accession NM\_022663) is another VGAM475 host target gene. CTAGE-1 BINDING SITE is

HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CTAGE-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CTAGE-1 BINDING SITE, designated SEQ ID:22910, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21853] Another function of VGAM475 is therefore inhibition of CTAGE-1 (Accession NM\_022663). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CTAGE-1. F-box Only Protein 9 (FBXO9, Accession NM\_033480) is another VGAM475 host target gene. FBXO9 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FBXO9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO9 BINDING SITE, designated SEQ ID:27255, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21854] Another function of VGAM475 is therefore inhibition of F-



box Only Protein 9 (FBXO9, Accession NM\_033480). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXO9. FLJ13322 (Accession NM\_024722) is another VGAM475 host target gene. FLJ13322 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13322 BINDING SITE, designated SEQ ID:24061, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21855] Another function of VGAM475 is therefore inhibition of FLJ13322 (Accession NM\_024722). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13322. FLJ13646 (Accession NM\_024584) is another VGAM475 host target gene. FLJ13646 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13646, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ13646 BINDING SITE, designated SEQ ID:23815, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21856] Another function of VGAM475 is therefore inhibition of FLJ13646 (Accession NM\_024584). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13646. FLJ20188 (Accession NM\_017703) is another VGAM475 host target gene. FLJ20188 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20188, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20188 BINDING SITE, designated SEQ ID:19277, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21857] Another function of VGAM475 is therefore inhibition of FLJ20188 (Accession NM\_017703). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20188. FLJ21032 (Accession NM\_024906) is another VGAM475

host target gene. FLJ21032 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21032 BINDING SITE, designated SEQ ID:24403, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21858] Another function of VGAM475 is therefore inhibition of FLJ21032 (Accession NM\_024906). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21032. FLJ23306 (Accession NM\_024530) is another VGAM475 host target gene. FLJ23306 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23306, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23306 BINDING SITE, designated SEQ ID:23733, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21859] Another function of VGAM475 is therefore inhibition of FLJ23306 (Accession NM\_024530). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23306. FYVE and Coiled-coil Domain Containing 1 (FYCO1, Accession NM\_024513) is another VGAM475 host target gene. FYCO1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FYCO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FYCO1 BINDING SITE, designated SEQ ID:23716, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21860] Another function of VGAM475 is therefore inhibition of FYVE and Coiled-coil Domain Containing 1 (FYCO1, Accession NM\_024513). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FYCO1. GMPPB (Accession XM\_171044) is another VGAM475 host target gene. GMPPB BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by

GMPPB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GMPPB BINDING SITE, designated SEQ ID:45816, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21861] Another function of VGAM475 is therefore inhibition of GMPPB (Accession XM\_171044). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GMPPB. HCC-4 (Accession NM\_138611) is another VGAM475 host target gene. HCC-4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HCC-4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCC-4 BINDING SITE, designated SEQ ID:28897, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21862] Another function of VGAM475 is therefore inhibition of HCC-4 (Accession NM\_138611). Accordingly, utilities of

VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCC-4. HM74 (Accession NM\_006018) is another VGAM475 host target gene. HM74 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HM74, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HM74 BINDING SITE, designated SEQ ID:12637, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21863] Another function of VGAM475 is therefore inhibition of HM74 (Accession NM\_006018). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HM74. HSPC063 (Accession NM\_014155) is another VGAM475 host target gene. HSPC063 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by HSPC063, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC063 BINDING SITE,

designated SEQ ID:15438, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21864] Another function of VGAM475 is therefore inhibition of HSPC063 (Accession NM\_014155). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC063. KIAA0247 (Accession NM\_014734) is another VGAM475 host target gene. KIAA0247 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0247, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0247 BINDING SITE, designated SEQ ID:16372, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21865] Another function of VGAM475 is therefore inhibition of KIAA0247 (Accession NM\_014734). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0247. KIAA0668 (Accession XM\_039332) is another VGAM475 host target gene. KIAA0668 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0668, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0668 BINDING SITE, designated SEQ ID:33049, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21866] Another function of VGAM475 is therefore inhibition of KIAA0668 (Accession XM\_039332). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0668. KIAA0669 (Accession NM\_014779) is another VGAM475 host target gene. KIAA0669 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0669, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0669 BINDING SITE, designated SEQ ID:16628, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21867] Another function of VGAM475 is therefore inhibition of



KIAA0669 (Accession NM\_014779). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0669. KIAA0710 (Accession NM\_014871) is another VGAM475 host target gene. KIAA0710 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0710, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0710 BINDING SITE, designated SEQ ID:16994, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21868] Another function of VGAM475 is therefore inhibition of KIAA0710 (Accession NM\_014871). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0710. KIAA0720 (Accession XM\_030970) is another VGAM475 host target gene. KIAA0720 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0720, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA0720 BINDING SITE, designated SEQ ID:31237, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21869] Another function of VGAM475 is therefore inhibition of KIAA0720 (Accession XM\_030970). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0720. KIAA1045 (Accession XM\_048592) is another VGAM475 host target gene. KIAA1045 BINDING SITE1 and KIAA1045 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KIAA1045, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1045 BINDING SITE1 and KIAA1045 BINDING SITE2, designated SEQ ID:35203 and SEQ ID:35204 respectively, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21870] Another function of VGAM475 is therefore inhibition of KIAA1045 (Accession XM\_048592). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1045. KIAA1337 (Accession XM\_052561) is another VGAM475 host target gene. KIAA1337 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1337 BINDING SITE, designated SEQ ID:35982, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21871] Another function of VGAM475 is therefore inhibition of KIAA1337 (Accession XM\_052561). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1337. KIAA1393 (Accession XM\_050793) is another VGAM475 host target gene. KIAA1393 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1393, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1393 BINDING SITE, designated SEQ ID:35683, to the

nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21872] Another function of VGAM475 is therefore inhibition of KIAA1393 (Accession XM\_050793). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1393. KIAA1854 (Accession XM\_049884) is another VGAM475 host target gene. KIAA1854 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1854, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1854 BINDING SITE, designated SEQ ID:35532, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21873] Another function of VGAM475 is therefore inhibition of KIAA1854 (Accession XM\_049884). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1854. KIAA1889 (Accession XM\_056298) is another VGAM475 host target gene. KIAA1889 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1889, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1889 BINDING SITE, designated SEQ ID:36385, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21874] Another function of VGAM475 is therefore inhibition of KIAA1889 (Accession XM\_056298). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1889. Lysophospholipase II (LYPLA2, Accession NM\_007260) is another VGAM475 host target gene. LY-PLA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LYPLA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LYPLA2 BINDING SITE, designated SEQ ID:14130, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21875] Another function of VGAM475 is therefore inhibition of

Lysophospholipase II (LYPLA2, Accession NM\_007260). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LYPLA2. Mab-21-like 2 (*C. elegans*) (MAB21L2, Accession NM\_006439) is another VGAM475 host target gene. MAB21L2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MAB21L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAB21L2 BINDING SITE, designated SEQ ID:13153, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21876] Another function of VGAM475 is therefore inhibition of Mab-21-like 2 (*C. elegans*) (MAB21L2, Accession NM\_006439). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAB21L2. MGC2654 (Accession NM\_024109) is another VGAM475 host target gene. MGC2654 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2654, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2654 BINDING SITE, designated SEQ ID:23555, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21877] Another function of VGAM475 is therefore inhibition of MGC2654 (Accession NM\_024109). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2654. Prostate Cancer Associated Protein 7 (PCANAP7, Accession XM\_167803) is another VGAM475 host target gene. PCANAP7 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PCANAP7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCANAP7 BINDING SITE, designated SEQ ID:44839, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21878] Another function of VGAM475 is therefore inhibition of Prostate Cancer Associated Protein 7 (PCANAP7, Accession

XM\_167803). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCANAP7. Phosphatidylserine Synthase 2 (PTDSS2, Accession NM\_030783) is another VGAM475 host target gene. PTDSS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTDSS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTDSS2 BINDING SITE, designated SEQ ID:25077, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21879] Another function of VGAM475 is therefore inhibition of Phosphatidylserine Synthase 2 (PTDSS2, Accession NM\_030783). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTDSS2. LOC115330 (Accession NM\_138445) is another VGAM475 host target gene. LOC115330 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115330, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING



SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115330 BINDING SITE, designated SEQ ID:28812, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21880] Another function of VGAM475 is therefore inhibition of LOC115330 (Accession NM\_138445). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115330. LOC124446 (Accession XM\_058805) is another VGAM475 host target gene. LOC124446 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC124446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124446 BINDING SITE, designated SEQ ID:36751, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21881] Another function of VGAM475 is therefore inhibition of LOC124446 (Accession XM\_058805). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC124446. LOC126299 (Accession XM\_059019) is another VGAM475 host target gene. LOC126299 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC126299, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126299 BINDING SITE, designated SEQ ID:36817, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21882] Another function of VGAM475 is therefore inhibition of LOC126299 (Accession XM\_059019). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126299. LOC133584 (Accession XM\_059661) is another VGAM475 host target gene. LOC133584 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133584, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133584 BINDING SITE, designated SEQ ID:37047, to the nucleotide sequence of VGAM475 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3186.

[21883] Another function of VGAM475 is therefore inhibition of LOC133584 (Accession XM\_059661). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133584. LOC144347 (Accession XM\_084832) is another VGAM475 host target gene. LOC144347 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144347, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144347 BINDING SITE, designated SEQ ID:37725, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21884] Another function of VGAM475 is therefore inhibition of LOC144347 (Accession XM\_084832). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144347. LOC147991 (Accession XM\_085993) is another VGAM475 host target gene. LOC147991 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147991, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147991 BINDING SITE, designated SEQ ID:38437, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21885] Another function of VGAM475 is therefore inhibition of LOC147991 (Accession XM\_085993). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147991. LOC149175 (Accession XM\_086445) is another VGAM475 host target gene. LOC149175 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149175, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149175 BINDING SITE, designated SEQ ID:38661, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21886] Another function of VGAM475 is therefore inhibition of LOC149175 (Accession XM\_086445). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC149175. LOC149301 (Accession XM\_086480) is another VGAM475 host target gene. LOC149301 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149301 BINDING SITE, designated SEQ ID:38687, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21887] Another function of VGAM475 is therefore inhibition of LOC149301 (Accession XM\_086480). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149301. LOC151584 (Accession XM\_098089) is another VGAM475 host target gene. LOC151584 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151584, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151584 BINDING SITE, designated SEQ ID:41374, to

the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21888] Another function of VGAM475 is therefore inhibition of LOC151584 (Accession XM\_098089). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151584. LOC158835 (Accession XM\_088683) is another VGAM475 host target gene. LOC158835 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158835, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158835 BINDING SITE, designated SEQ ID:39896, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21889] Another function of VGAM475 is therefore inhibition of LOC158835 (Accession XM\_088683). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158835. LOC164397 (Accession XM\_092780) is another VGAM475 host target gene. LOC164397 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC164397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164397 BINDING SITE, designated SEQ ID:40155, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21890] Another function of VGAM475 is therefore inhibition of LOC164397 (Accession XM\_092780). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC164397. LOC166929 (Accession XM\_094192) is another VGAM475 host target gene. LOC166929 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC166929, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC166929 BINDING SITE, designated SEQ ID:40224, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21891] Another function of VGAM475 is therefore inhibition of LOC166929 (Accession XM\_094192). Accordingly, utilities

of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC166929. LOC169026 (Accession XM\_095471) is another VGAM475 host target gene. LOC169026 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC169026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169026 BINDING SITE, designated SEQ ID:40262, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21892] Another function of VGAM475 is therefore inhibition of LOC169026 (Accession XM\_095471). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC169026. LOC201194 (Accession XM\_117061) is another VGAM475 host target gene. LOC201194 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC201194, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences



of LOC201194 BINDING SITE, designated SEQ ID:43219, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21893] Another function of VGAM475 is therefore inhibition of LOC201194 (Accession XM\_117061). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201194. LOC221683 (Accession XM\_168089) is another VGAM475 host target gene. LOC221683 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221683, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221683 BINDING SITE, designated SEQ ID:45005, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21894] Another function of VGAM475 is therefore inhibition of LOC221683 (Accession XM\_168089). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221683. LOC222488 (Accession XM\_169440) is another VGAM475 host target gene. LOC222488 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC222488, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222488 BINDING SITE, designated SEQ ID:45301, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21895] Another function of VGAM475 is therefore inhibition of LOC222488 (Accession XM\_169440). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222488. LOC253613 (Accession XM\_171225) is another VGAM475 host target gene. LOC253613 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC253613, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253613 BINDING SITE, designated SEQ ID:46008, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21896] Another function of VGAM475 is therefore inhibition of

LOC253613 (Accession XM\_171225). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253613. LOC254423 (Accession XM\_173286) is another VGAM475 host target gene. LOC254423 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254423 BINDING SITE, designated SEQ ID:46530, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21897] Another function of VGAM475 is therefore inhibition of LOC254423 (Accession XM\_173286). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254423. LOC255045 (Accession XM\_171243) is another VGAM475 host target gene. LOC255045 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255045, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC255045 BINDING SITE, designated SEQ ID:46035, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21898] Another function of VGAM475 is therefore inhibition of LOC255045 (Accession XM\_171243). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255045. LOC257153 (Accession XM\_171047) is another VGAM475 host target gene. LOC257153 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257153, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257153 BINDING SITE, designated SEQ ID:45826, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21899] Another function of VGAM475 is therefore inhibition of LOC257153 (Accession XM\_171047). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257153. LOC51667 (Accession NM\_016118) is an-

other VGAM475 host target gene. LOC51667 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51667, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51667 BINDING SITE, designated SEQ ID:18198, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21900] Another function of VGAM475 is therefore inhibition of LOC51667 (Accession NM\_016118). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51667. LOC55901 (Accession NM\_018676) is another VGAM475 host target gene. LOC55901 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC55901, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC55901 BINDING SITE, designated SEQ ID:20750, to the nucleotide sequence of VGAM475 RNA, herein designated VGAM RNA, also designated SEQ ID:3186.

[21901] Another function of VGAM475 is therefore inhibition of LOC55901 (Accession NM\_018676). Accordingly, utilities of VGAM475 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC55901. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 476 (VGAM476) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21902] VGAM476 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM476 was detected is described hereinabove with reference to Figs. 1–8.

[21903] VGAM476 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tick-borne Encephalitis Virus. VGAM476 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21904] VGAM476 gene encodes a VGAM476 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM476

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM476 precursor RNA is designated SEQ ID:462, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:462 is located at position 8886 relative to the genome of Tick-borne Encephalitis Virus.

[21905] VGAM476 precursor RNA folds onto itself, forming VGAM476 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21906] An enzyme complex designated DICER COMPLEX, `dices` the VGAM476 folded precursor RNA into VGAM476 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 43%) nucleotide sequence of VGAM476 RNA is designated SEQ ID:3187, and is provided hereinbelow with reference to the sequence listing part.

[21907] VGAM476 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM476 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM476 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[21908] VGAM476 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM476 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM476 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the



number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM476 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM476 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21909] The complementary binding of VGAM476 RNA, herein designated VGAM RNA, to host target binding sites on VGAM476 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM476 host target RNA into VGAM476 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21910] It is appreciated that VGAM476 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM476 host target genes. The mRNA of each one of this plurality of VGAM476 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM476 RNA, herein designated VGAM RNA, and which when bound by VGAM476 RNA causes inhibition of translation of respective one or more VGAM476 host target proteins.

[21911] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM476 gene, herein designated VGAM GENE, on one or more VGAM476 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21912] It is yet further appreciated that a function of VGAM476 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of viral infection by Tick-borne Encephalitis Virus. Specific functions, and accordingly utilities, of VGAM476 correlate with, and may be deduced from, the identity of the host target genes which VGAM476 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[21913] Nucleotide sequences of the VGAM476 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM476 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM476 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM476 are further described hereinbelow with reference to Table 1.

[21914] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM476 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM476 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[21915] As mentioned hereinabove with reference to Fig. 1, a function of VGAM476 gene, herein designated VGAM is inhibition of expression of VGAM476 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM476 correlate with, and may be deduced from, the identity of the target genes which VGAM476 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21916] BRF1 Homolog, Subunit of RNA Polymerase III Transcription Initiation Factor IIIB (*S. cerevisiae*) (BRF1, Accession NM\_001519) is a VGAM476 host target gene. BRF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BRF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BRF1 BINDING SITE, designated SEQ ID:7255, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21917] A function of VGAM476 is therefore inhibition of BRF1 Homolog, Subunit of RNA Polymerase III Transcription Initiation Factor IIIB (*S. cerevisiae*) (BRF1, Accession

NM\_001519), a gene which is a general activator of RNA polymerase III. Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BRF1. The function of BRF1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM232.Chemokine (C-X3-C motif) Receptor 1

(CX3CR1, Accession XM\_047502) is another VGAM476 host target gene. CX3CR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CX3CR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CX3CR1 BINDING SITE, designated SEQ ID:34982, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21918] Another function of VGAM476 is therefore inhibition of Chemokine (C-X3-C motif) Receptor 1 (CX3CR1, Accession XM\_047502), a gene which mediates both the adhesive and migratory functions of fractalkine. Accordingly, utilities of VGAM476 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with CX3CR1. The function of CX3CR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM25. Glucocorticoid Receptor DNA Binding Factor 1 (GRLF1, Accession XM\_085943) is another VGAM476 host target gene. GRLF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRLF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRLF1 BINDING SITE, designated SEQ ID:38409, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21919] Another function of VGAM476 is therefore inhibition of Glucocorticoid Receptor DNA Binding Factor 1 (GRLF1, Accession XM\_085943), a gene which inhibits transcription of the glucocorticoid receptor gene. Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRLF1. The function of GRLF1 and its association with various diseases and clinical conditions, has been established by

previous studies, as described hereinabove with reference to VGAM55. Potassium Voltage-gated Channel, Shaw-related Subfamily, Member 3 (KCNC3, Accession NM\_004977) is another VGAM476 host target gene. KCNC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNC3 BINDING SITE, designated SEQ ID:11420, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21920] Another function of VGAM476 is therefore inhibition of Potassium Voltage-gated Channel, Shaw-related Subfamily, Member 3 (KCNC3, Accession NM\_004977), a gene which mediates the voltage-dependent potassium ion permeability of excitable membranes. Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNC3. The function of KCNC3 has been established by previous studies. Several genes (the Shaker or Sh gene family) encoding components of voltage-gated K(+) chan-

nels have been identified in various species. Based on sequence similarities, Sh genes are classified into 4 groups or subfamilies. Mammalian genes of each one of these subfamilies also show high levels of sequence similarity to 1 of 4 related *Drosophila* genes: Shaker, Shab, Shaw, and Shal. By fluorescence in situ hybridization, Ried et al. (1993) showed that the gene encoding a Shaw-related product previously studied in rat and mouse maps to 11p15 in a region that shows homology of synteny with a region of mouse chromosome 7. Because the prolonged QT syndrome (OMIM Ref. No. 192500) maps to this same region and because of pathophysiologic plausibility, mutations in the KCNC1 gene should be sought in that disorder. Grissmer et al. (1992) mapped the gene for the Shaw-related potassium channel in T cells to chromosome 11. This was referred to as Kv3.1. The related Kv1.1 and Kv3.2 genes were localized to chromosome 12, while the ISK gene (OMIM Ref. No. 176261) mapped to chromosome 21. Stubbs et al. (1994) established a long-range physical map of the region of mouse chromosome 7 containing 6 genes located within a 500-kb interval just proximal of the pink-eyed dilution (p) locus (OMIM Ref. No. 203200): Ldh1 (OMIM Ref. No. 150000), Ldh3 (OMIM Ref. No.



150150), Saa (OMIM Ref. No. 104750), Tph (OMIM Ref. No. 191060), Kcnc1, and Myod1 (OMIM Ref. No. 159970). The findings, together with mapping studies within the related region of human 11p15, demonstrated that gene content and organization within this homology segment had been highly conserved throughout evolution.

[21921] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21922] Ried, T.; Rudy, B.; Vega-Saenz de Miera, E.; Lau, D.; Ward, D. C.; Sen, K. : Localization of a highly conserved human potassium channel gene (NGK2-KV4; KCNC1) to chromosome 11p15. Genomics 15: 405-411, 1993. ; and

[21923] Stubbs, L.; Rinchik, E. M.; Goldberg, E.; Rudy, B.; Handel, M. A.; Johnson, D. : Clustering of six human 11p15 gene homologs within a 500-kb interval of proximal mouse chromosome 7. Gen.

[21924] Further studies establishing the function and utilities of KCNC3 are found in John Hopkins OMIM database record ID 176264, and in cited publications numbered 10927 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Potassium Inwardly-rectifying Channel, Subfamily J, Member 10

(KCNJ10, Accession NM\_002241) is another VGAM476 host target gene. KCNJ10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNJ10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNJ10 BINDING SITE, designated SEQ ID:8024, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21925] Another function of VGAM476 is therefore inhibition of Potassium Inwardly-rectifying Channel, Subfamily J, Member 10 (KCNJ10, Accession NM\_002241), a gene which may be responsible for potassium buffering action of glial cells in the brain. Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNJ10. The function of KCNJ10 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM167. Latent Transforming Growth Factor Beta Binding Protein 2 (LTBP2, Accession NM\_000428) is another VGAM476 host target gene. LTBP2 BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by LTBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LTBP2 BINDING SITE, designated SEQ ID:6004, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21926] Another function of VGAM476 is therefore inhibition of Latent Transforming Growth Factor Beta Binding Protein 2 (LTBP2, Accession NM\_000428), a gene which targets latent TGF-beta to the extracellular matrix. Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LTBP2. The function of LTBP2 has been established by previous studies. Transforming growth factors (TGFs) beta-1 (OMIM Ref. No. 190180), beta-2 (OMIM Ref. No. 190220), beta-3 (OMIM Ref. No. 190230), and others have both stimulatory and inhibitory effects on the growth of different cell types and play a role in the production and degradation of the extracellular matrix. TGF-beta molecules are secreted in the form of latent large molecular mass complexes that contain other proteins, such as

latent TGF-beta-1 binding protein (LTBP1; 150390). There is evidence that these binding proteins modulate TGF-beta bioavailability. Animal model experiments lend further support to the function of LTBP2. Dabovic et al. (2002) created an *Ltbp3*-null mutation in the mouse by gene targeting. Mice homozygous for the mutation developed craniofacial malformations by day 10. At 2 months, there was a pronounced rounding of the cranial vault, extension of the mandible beyond the maxilla, and kyphosis. Between 6 and 9 months of age, mutant mice also developed osteosclerosis and osteoarthritis. The pathologic changes were consistent with perturbed TGF-beta signaling in the skull and long bones

[21927] It is appreciated that the abovementioned animal model for LTBP2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21928] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21929] Oklu, R.; Hesketh, R. : The latent transforming growth factor beta binding protein (LTBP) family. *Biochem. J.* 352: 601-610, 2000. ; and

[21930] Dabovic, B.; Chen, Y.; Colarossi, C.; Obata, H.; Zambuto, L.; Perle, M. A.; Rifkin, D. B. : Bone abnormalities in latent TGF-beta binding protein (Ltbp)-3-null mice indicate a role for Ltb.

[21931] Further studies establishing the function and utilities of LTBP2 are found in John Hopkins OMIM database record ID 602090, and in cited publications numbered 6357-635 and 12464-6360 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540) is another VGAM476 host target gene. ODF2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ODF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ODF2 BINDING SITE, designated SEQ ID:8385, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21932] Another function of VGAM476 is therefore inhibition of Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540), a gene which is very strongly similar to rat Odf2 . Accordingly, utilities of VGAM476 include diagno-

sis, prevention and treatment of diseases and clinical conditions associated with ODF2. The function of ODF2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM363. Periaxin (PRX, Accession NM\_020956) is another VGAM476 host target gene. PRX BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRX BINDING SITE, designated SEQ ID:21941, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21933] Another function of VGAM476 is therefore inhibition of Periaxin (PRX, Accession NM\_020956), a gene which seems to be required for maintenance of peripheral nerve myelin sheath. may have a role in axon-glial interactions, possibly by interacting with the cytoplasmic domains of integral membrane proteins such as myelin-associated glycoprotein in the periaxonal regions of the schwann cell plasma membrane. may have a role in the early phases of myelin deposition. Accordingly, utilities of VGAM476 in-

clude diagnosis, prevention and treatment of diseases and clinical conditions associated with PRX. The function of PRX has been established by previous studies. The periaxin gene (PRX) encodes 2 PDZ-domain proteins, L- and S-periaxin, that are required for maintenance of peripheral nerve myelin. The PDZ domain, which consists of a nearly 90-amino acid protein-binding motif that interacts with the C termini of plasma membrane proteins and with the cortical cytoskeleton, has been implicated in the assembly of signaling complexes at sites of cell-cell contact. By FISH and electronic PCR (Schuler, 1997), Boerkoel et al. (2001) mapped the PRX gene between D19S324 and D19S223 within a BAC on 19q13.1-q13.2, a position showing conserved synteny with mouse chromosome 7 where the Prx gene maps (Gillespie et al., 1997). They pointed out that the interactions among L-periaxin, the cytoskeleton, and a membrane complex are reminiscent of the interactions among the proteins of the dystrophin-sarcoglycan complex (Cohn and Campbell, 2000) and the signaling complexes organized by other PDZ domain proteins. They hypothesized that mutations in cytoskeletal and membrane proteins interacting with L-periaxin may also cause Charcot-Marie-Tooth disease or related neu-

ropathies. In 3 unrelated patients with Dejerine–Sottas neuropathy (OMIM Ref. No. 145900), Boerkoel et al. (2001) identified recessive mutations in the PRX gene (605725.0001–605725.004). They mapped recessive Dejerine–Sottas neuropathy to 19q13.1–q13.2, a region associated with a severe autosomal recessive demyelinating neuropathy in a Lebanese family reported by Delague et al. (2000) as Charcot–Marie–Tooth disease type 4F. Animal model experiments lend further support to the function of PRX. Confirming the necessity of periaxin for maintenance of the myelin sheath, Gillespie et al. (2000) demonstrated that Prx  $-/-$  mice ensheath and myelinate peripheral axons apparently normally but subsequently develop a severe demyelinating neuropathy associated with allodynia (pain from non-noxious stimuli) and hyperalgesia (hypersensitivity to pain).

[21934] It is appreciated that the abovementioned animal model for PRX is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[21935] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:



[21936] Takashima, H.; Boerkoel, C. F.; De Jonghe, P.; Ceuterick, C.; Martin, J.-J.; Voit, T.; Schroder, J.-M.; Williams, A.; Brophy, P. J.; Timmerman, V.; Lupski, J. R. : Periaxin mutations cause a broad spectrum of demyelinating neuropathies. *Ann. Neurol.* 51: 709–715, 2002. ; and

[21937] Boerkoel, C. F.; Takashima, H.; Stankiewicz, P.; Garcia, C. A.; Leber, S. M.; Rhee-Morris, L.; Lupski, J. R. : Periaxin mutations cause recessive Dejerine-Sottas neuropathy. *Am. J. Hum.*

[21938] Further studies establishing the function and utilities of PRX are found in John Hopkins OMIM database record ID 605725, and in cited publications numbered 3546, 6910, 6911–6912, 355 and 6913–6914 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ribosomal Protein L10 (RPL10, Accession NM\_006013) is another VGAM476 host target gene. RPL10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RPL10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RPL10 BINDING SITE, designated SEQ ID:12623, to the nucleotide sequence of VGAM476 RNA,

herein designated VGAM RNA, also designated SEQ ID:3187.

[21939] Another function of VGAM476 is therefore inhibition of Ribosomal Protein L10 (RPL10, Accession NM\_006013), a gene which may be a component of the 60S ribosomal subunit. Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RPL10. The function of RPL10 has been established by previous studies. Weissman et al. (1987) provided a functional assay for the identification of the suppressor gene(s) involved in Wilms tumor, by showing that introduction of a normal chromosome 11 into a Wilms tumor cell line completely abolished its tumorigenic action in nude mice. Dowdy et al. (1991) showed that this suppressor activity resided in the 11p15 and not in the 11p13 region; see Wilms tumor, type II (WT2; 194071). In an attempt to isolate a suppressor gene, Dowdy et al. (1991) performed a subtractive hybridization assay with the tumorigenic Wilms tumor cell line and its nontumorigenic derivative which contained an extra t(X;11) translocation chromosome. A single novel cDNA clone, designated QM, was identified and, as the QM mRNA was modulated between tumorigenic and nontumorigenic cell

lines, the QM gene was an attractive tumor-suppressor candidate gene. In the course of investigating disease genes in the Xqter region, van den Ouweland et al. (1992) found a cosmid that appeared to harbor the QM gene as it demonstrated 100% identity with the cDNA sequence published by Dowdy et al. (1991). With an exon-specific polymerase chain reaction, van den Ouweland et al. (1992) demonstrated that the genomic homolog of the QM cDNA is located in Xq28 in the region of the G6PD and color vision genes. No homologous sequences could be detected on 11p. Thus, the QM gene is not, per se, involved in the suppression of Wilms tumor. QM is a 214-amino acid polypeptide encoded by a gene previously designated DXS648. It contains a high percentage of charged amino acids and binds to the JUN oncogene (OMIM Ref. No. 165160) and to DNA. Although they found no matches between QM and any other known transcription factors in searches of DNA databases, Farmer et al. (1994) found a high degree of conservation throughout the first 175 residues of the protein when studies were performed on a diverse array of eukaryotes. Most notable was the considerable conservation of charged amino acids within specific regions. The rate of sequence divergence of the various

homologs was found to be slow, of the order of 1% change every 22 million years, consistent with a critical role of QM in eukaryotic cells. Farmer et al. (1994) suggested that QM belongs to a novel class of transcription regulatory proteins.

[21940] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21941] Dowdy, S. F.; Fasching, C. L.; Araujo, D.; Lai, K.-M.; Livanos, E.; Weissman, B. E.; Stanbridge, E. J. : Suppression of tumorigenicity in Wilms' tumor by the p15.5-p14 region of chromosome 11. Science 254: 293-295, 1991. ; and

[21942] Farmer, A. A.; Loftus, T. M.; Mills, A. A.; Sato, K. Y.; Neill, J. D.; Tron, T.; Yang, M.; Trumpower, B. L.; Stanbridge, E. J. : Extreme evolutionary conservation of QM, a novel c-Jun assoc.

[21943] Further studies establishing the function and utilities of RPL10 are found in John Hopkins OMIM database record ID 312173, and in cited publications numbered 8388-8394 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cyclin M1 (CNNM1, Accession NM\_020348) is another VGAM476

host target gene. CNNM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNNM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNNM1 BINDING SITE, designated SEQ ID:21606, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21944] Another function of VGAM476 is therefore inhibition of Cyclin M1 (CNNM1, Accession NM\_020348). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNNM1. DKFZP434N1511 (Accession XM\_166138) is another VGAM476 host target gene. DKFZP434N1511 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434N1511, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434N1511 BINDING SITE, designated SEQ ID:43934, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3187.

[21945] Another function of VGAM476 is therefore inhibition of DKFZP434N1511 (Accession XM\_166138). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434N1511. FLJ12770 (Accession NM\_032174) is another VGAM476 host target gene. FLJ12770 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12770, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12770 BINDING SITE, designated SEQ ID:25884, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21946] Another function of VGAM476 is therefore inhibition of FLJ12770 (Accession NM\_032174). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12770. FLJ13964 (Accession NM\_032186) is another VGAM476 host target gene. FLJ13964 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13964, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13964 BINDING SITE, designated SEQ ID:25901, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21947] Another function of VGAM476 is therefore inhibition of FLJ13964 (Accession NM\_032186). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13964. FLJ20040 (Accession NM\_018992) is another VGAM476 host target gene. FLJ20040 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20040 BINDING SITE, designated SEQ ID:21065, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21948] Another function of VGAM476 is therefore inhibition of FLJ20040 (Accession NM\_018992). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ20040. FLJ22551 (Accession NM\_024708) is another VGAM476 host target gene. FLJ22551 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ22551, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22551 BINDING SITE, designated SEQ ID:24025, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21949] Another function of VGAM476 is therefore inhibition of FLJ22551 (Accession NM\_024708). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22551. KIAA0084 (Accession XM\_042841) is another VGAM476 host target gene. KIAA0084 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0084, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0084 BINDING SITE, designated SEQ ID:33805, to the nucleotide sequence of



VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21950] Another function of VGAM476 is therefore inhibition of KIAA0084 (Accession XM\_042841). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0084. KIAA0806 (Accession NM\_014813) is another VGAM476 host target gene. KIAA0806 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0806, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0806 BINDING SITE, designated SEQ ID:16779, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21951] Another function of VGAM476 is therefore inhibition of KIAA0806 (Accession NM\_014813). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0806. KIAA1950 (Accession XM\_166532) is another VGAM476 host target gene. KIAA1950 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1950, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1950 BINDING SITE, designated SEQ ID:44483, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21952] Another function of VGAM476 is therefore inhibition of KIAA1950 (Accession XM\_166532). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1950. Protein Tyrosine Phosphatase, Receptor Type, F Polypeptide (PTPRF), Interacting Protein (liprin), Alpha 4 (PPFIA4, Accession XM\_046751) is another VGAM476 host target gene. PPFIA4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPFIA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPFIA4 BINDING SITE, designated SEQ ID:34819, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21953] Another function of VGAM476 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, F Polypeptide (PTPRF), Interacting Protein (liprin), Alpha 4 (PPFIA4, Accession XM\_046751). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPFIA4. SSB-3 (Accession NM\_080861) is another VGAM476 host target gene. SSB-3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSB-3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSB-3 BINDING SITE, designated SEQ ID:28100, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21954] Another function of VGAM476 is therefore inhibition of SSB-3 (Accession NM\_080861). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSB-3. LOC115051 (Accession XM\_010647) is another VGAM476 host target gene. LOC115051 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115051, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115051 BINDING SITE, designated SEQ ID:30159, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21955] Another function of VGAM476 is therefore inhibition of LOC115051 (Accession XM\_010647). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115051. LOC127845 (Accession XM\_059186) is another VGAM476 host target gene. LOC127845 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC127845, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127845 BINDING SITE, designated SEQ ID:36911, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21956] Another function of VGAM476 is therefore inhibition of LOC127845 (Accession XM\_059186). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC127845. LOC158056 (Accession XM\_088463) is another VGAM476 host target gene. LOC158056 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158056 BINDING SITE, designated SEQ ID:39714, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21957] Another function of VGAM476 is therefore inhibition of LOC158056 (Accession XM\_088463). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158056. LOC196955 (Accession XM\_085210) is another VGAM476 host target gene. LOC196955 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196955, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196955 BINDING SITE, designated SEQ ID:37927, to

the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21958] Another function of VGAM476 is therefore inhibition of LOC196955 (Accession XM\_085210). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196955. LOC256158 (Accession XM\_175125) is another VGAM476 host target gene. LOC256158 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256158, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256158 BINDING SITE, designated SEQ ID:46619, to the nucleotide sequence of VGAM476 RNA, herein designated VGAM RNA, also designated SEQ ID:3187.

[21959] Another function of VGAM476 is therefore inhibition of LOC256158 (Accession XM\_175125). Accordingly, utilities of VGAM476 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256158. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 477 (VGAM477) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21960] VGAM477 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM477 was detected is described hereinabove with reference to Figs. 1–8.

[21961] VGAM477 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM477 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[21962] VGAM477 gene encodes a VGAM477 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM477 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM477 precursor RNA is designated SEQ ID:463, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:463 is located at position 6061 relative to the genome of Hepatitis G Virus.

[21963] VGAM477 precursor RNA folds onto itself, forming VGAM477 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21964] An enzyme complex designated DICER COMPLEX, `dices` the VGAM477 folded precursor RNA into VGAM477 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM477 RNA is designated SEQ ID:3188, and is provided hereinbelow with reference to the sequence listing part.

[21965] VGAM477 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM477 host target RNA, herein designated VGAM



HOST TARGET RNA. VGAM477 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[21966] VGAM477 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM477 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM477 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM477 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM477 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[21967] The complementary binding of VGAM477 RNA, herein designated VGAM RNA, to host target binding sites on VGAM477 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM477 host target RNA into VGAM477 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[21968] It is appreciated that VGAM477 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM477 host target genes. The mRNA of each one of this plurality of VGAM477 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM477 RNA, herein designated VGAM RNA, and which when bound by VGAM477 RNA causes inhibition of translation of respective one or more VGAM477 host target proteins.

[21969] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM477 gene, herein designated VGAM GENE, on one or more VGAM477 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[21970] It is yet further appreciated that a function of VGAM477 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM477 correlate with, and may be deduced from, the identity of the host

target genes which VGAM477 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [21971] Nucleotide sequences of the VGAM477 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM477 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM477 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM477 are further described hereinbelow with reference to Table 1.
- [21972] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM477 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM477 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [21973] As mentioned hereinabove with reference to Fig. 1, a function of VGAM477 gene, herein designated VGAM is inhibition of expression of VGAM477 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM477 correlate with, and may be deduced from, the identity of the target genes which VGAM477

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[21974] Adenylate Cyclase 9 (ADCY9, Accession NM\_001116) is a VGAM477 host target gene. ADCY9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADCY9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADCY9 BINDING SITE, designated SEQ ID:6791, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21975] A function of VGAM477 is therefore inhibition of Adenylate Cyclase 9 (ADCY9, Accession NM\_001116), a gene which . may be a physiologically relevant docking site for calcineurin (by similarity). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADCY9. The function of ADCY9 has been established by previous studies. The adenylyl cyclases (EC 4.6.1.1) are membrane-associated enzymes that are expressed in most human tissues. These enzymes catalyze the formation of cAMP and are regulated by a family of G protein-coupled recep-

tors, protein kinases, and calcium. The type 9 adenylyl cyclase (ADCY9) is a widely distributed adenylyl cyclase that was originally cloned from mouse (Paterson et al., 1995; Premont et al., 1996). Hacker et al. (1998) cloned human cardiac ADCY9, or AC9, cDNAs and found that the deduced 1,294-amino acid protein is 90% identical to mouse Adcy9. Like mouse Adcy9, the predicted human ADCY9 protein contains 12 transmembrane domains, Asn-linked glycosylation sites, and cAMP-dependent protein kinase phosphorylation sites; however, these proteins differ in the C2b domain due to a frameshift in the human ADCY9 coding sequence relative to the coding sequence of mouse Adcy9. Northern blot analysis detected 8.5- and 6.3-kb ADCY9 transcripts in all human tissues examined. By fluorescence in situ hybridization, Hacker et al. (1998) mapped the human and mouse ADCY9 genes to 16p13.3 and chromosome 16 band B1, respectively.

[21976] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[21977] Premont, R. T.; Matsuoka, I.; Mattei, M. G.; Pouille, Y.; Defer, N.; Hanoune, J. : Identification and characterization of a widely expressed form of adenylyl cyclase. *J. Biol. Chem.*

271: 13900–13907, 1996. ; and

[21978] Hacker, B. M.; Tomlinson, J. E.; Wayman, G. A.; Sultana, R.; Chan, G.; Villacres, E.; Disteché, C.; Storm, D. R. : Cloning, chromosomal mapping, and regulatory properties of the human ty.

[21979] Further studies establishing the function and utilities of ADCY9 are found in John Hopkins OMIM database record ID 603302, and in cited publications numbered 2438–2441 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104) is another VGAM477 host target gene. BACE BINDING SITE1 and BACE BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by BACE, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACE BINDING SITE1 and BACE BINDING SITE2, designated SEQ ID:14414 and SEQ ID:29082 respectively, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21980] Another function of VGAM477 is therefore inhibition of Beta-site APP-cleaving Enzyme (BACE, Accession

NM\_012104), a gene which is responsible for the proteolytic processing of the amyloid precursor protein. Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACE. The function of BACE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM173. Fibroblast Growth Factor Receptor-like 1 (FGFRL1, Accession NM\_021923) is another VGAM477 host target gene. FGFRL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FGFRL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGFRL1 BINDING SITE, designated SEQ ID:22449, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21981] Another function of VGAM477 is therefore inhibition of Fibroblast Growth Factor Receptor-like 1 (FGFRL1, Accession NM\_021923). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGFRL1. COAS3



(Accession NM\_139020) is another VGAM477 host target gene. COAS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COAS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COAS3 BINDING SITE, designated SEQ ID:29120, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21982] Another function of VGAM477 is therefore inhibition of COAS3 (Accession NM\_139020). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COAS3. FLJ00058 (Accession XM\_086123) is another VGAM477 host target gene. FLJ00058 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ00058, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ00058 BINDING SITE, designated SEQ ID:38507, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3188.

[21983] Another function of VGAM477 is therefore inhibition of FLJ00058 (Accession XM\_086123). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00058. KIAA0446 (Accession XM\_044155) is another VGAM477 host target gene. KIAA0446 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0446 BINDING SITE, designated SEQ ID:34147, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21984] Another function of VGAM477 is therefore inhibition of KIAA0446 (Accession XM\_044155). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0446. KIAA0563 (Accession NM\_014834) is another VGAM477 host target gene. KIAA0563 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0563, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0563 BINDING SITE, designated SEQ ID:16844, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21985] Another function of VGAM477 is therefore inhibition of KIAA0563 (Accession NM\_014834). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0563. KIAA1550 (Accession XM\_039393) is another VGAM477 host target gene. KIAA1550 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1550, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1550 BINDING SITE, designated SEQ ID:33066, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21986] Another function of VGAM477 is therefore inhibition of KIAA1550 (Accession XM\_039393). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1550. KIAA1884 (Accession XM\_055539) is another VGAM477 host target gene. KIAA1884 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1884, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1884 BINDING SITE, designated SEQ ID:36290, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21987] Another function of VGAM477 is therefore inhibition of KIAA1884 (Accession XM\_055539). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1884. MGC12921 (Accession XM\_033362) is another VGAM477 host target gene. MGC12921 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC12921, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC12921 BINDING SITE, designated SEQ ID:31898, to

the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21988] Another function of VGAM477 is therefore inhibition of MGC12921 (Accession XM\_033362). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC12921. RA-GEF-2 (Accession NM\_016340) is another VGAM477 host target gene. RA-GEF-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RA-GEF-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RA-GEF-2 BINDING SITE, designated SEQ ID:18463, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21989] Another function of VGAM477 is therefore inhibition of RA-GEF-2 (Accession NM\_016340). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RA-GEF-2. LOC147071 (Accession XM\_054031) is another VGAM477 host target gene. LOC147071 BINDING SITE is HOST TARGET binding site found in the 5' untranslated

region of mRNA encoded by LOC147071, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147071 BINDING SITE, designated SEQ ID:36139, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21990] Another function of VGAM477 is therefore inhibition of LOC147071 (Accession XM\_054031). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147071. LOC154141 (Accession XM\_098482) is another VGAM477 host target gene. LOC154141 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154141, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154141 BINDING SITE, designated SEQ ID:41686, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21991] Another function of VGAM477 is therefore inhibition of LOC154141 (Accession XM\_098482). Accordingly, utilities

of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154141. LOC201173 (Accession XM\_113312) is another VGAM477 host target gene. LOC201173 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC201173, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201173 BINDING SITE, designated SEQ ID:42218, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21992] Another function of VGAM477 is therefore inhibition of LOC201173 (Accession XM\_113312). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201173. LOC201220 (Accession XM\_113321) is another VGAM477 host target gene. LOC201220 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC201220, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC201220 BINDING SITE, designated SEQ ID:42227, to the nucleotide sequence of VGAM477 RNA, herein designated VGAM RNA, also designated SEQ ID:3188.

[21993] Another function of VGAM477 is therefore inhibition of LOC201220 (Accession XM\_113321). Accordingly, utilities of VGAM477 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201220. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 478 (VGAM478) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[21994] VGAM478 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM478 was detected is described hereinabove with reference to Figs. 1–8.

[21995] VGAM478 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM478 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.



[21996] VGAM478 gene encodes a VGAM478 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM478 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM478 precursor RNA is designated SEQ ID:464, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:464 is located at position 8794 relative to the genome of Hepatitis G Virus.

[21997] VGAM478 precursor RNA folds onto itself, forming VGAM478 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[21998] An enzyme complex designated DICER COMPLEX, `dices` the VGAM478 folded precursor RNA into VGAM478 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM478 RNA is designated SEQ ID:3189, and is provided hereinbelow with reference to the sequence listing part.

[21999] VGAM478 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM478 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM478 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22000] VGAM478 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM478 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM478 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM478 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM478 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22001] The complementary binding of VGAM478 RNA, herein designated VGAM RNA, to host target binding sites on VGAM478 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM478 host target RNA into VGAM478 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22002] It is appreciated that VGAM478 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM478 host target genes. The mRNA of each one of this plurality of VGAM478 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM478 RNA, herein designated VGAM RNA, and which when bound by VGAM478 RNA causes inhibition of translation of respective one or more VGAM478 host target proteins.

[22003] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM478 gene, herein designated VGAM GENE, on one or more VGAM478 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[22004] It is yet further appreciated that a function of VGAM478 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM478 correlate with, and may be deduced from, the identity of the host target genes which VGAM478 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22005] Nucleotide sequences of the VGAM478 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM478 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM478 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM478 are further described hereinbelow with reference to Table 1.

[22006] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM478 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM478 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22007] As mentioned hereinabove with reference to Fig. 1, a function of VGAM478 gene, herein designated VGAM is inhibition of expression of VGAM478 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM478 correlate with, and may be deduced from, the identity of the target genes which VGAM478 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22008] ATPase, Cu<sup>++</sup> Transporting, Beta Polypeptide (Wilson disease) (ATP7B, Accession NM\_000053) is a VGAM478 host target gene. ATP7B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP7B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP7B BINDING SITE, designated SEQ ID:5504, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22009] A function of VGAM478 is therefore inhibition of ATPase, Cu++ Transporting, Beta Polypeptide (Wilson disease) (ATP7B, Accession NM\_000053). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP7B. Multiple Endocrine Neoplasia I (MEN1, Accession NM\_130804) is another VGAM478 host target gene. MEN1 BINDING SITE1 through MEN1 BINDING SITE7 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MEN1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEN1 BINDING SITE1 through MEN1 BINDING SITE7, designated SEQ ID:28300, SEQ ID:5773, SEQ ID:28287, SEQ ID:28289, SEQ ID:28291, SEQ ID:28293 and SEQ ID:28296 respectively, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22010] Another function of VGAM478 is therefore inhibition of Multiple Endocrine Neoplasia I (MEN1, Accession NM\_130804). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEN1. DKFZp762E1511

(Accession XM\_003460) is another VGAM478 host target gene. DKFZp762E1511 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp762E1511, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762E1511 BINDING SITE, designated SEQ ID:29930, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22011] Another function of VGAM478 is therefore inhibition of DKFZp762E1511 (Accession XM\_003460). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp762E1511. FLJ20312 (Accession NM\_017761) is another VGAM478 host target gene. FLJ20312 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20312, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20312 BINDING SITE, designated SEQ ID:19375, to the nucleotide sequence of VGAM478 RNA, herein designated



VGAM RNA, also designated SEQ ID:3189.

[22012] Another function of VGAM478 is therefore inhibition of FLJ20312 (Accession NM\_017761). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20312. KIAA1239 (Accession XM\_049078) is another VGAM478 host target gene. KIAA1239 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1239, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1239 BINDING SITE, designated SEQ ID:35339, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22013] Another function of VGAM478 is therefore inhibition of KIAA1239 (Accession XM\_049078). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1239. Peptidylprolyl Isomerase (cyclophilin)-like 3 (PPIL3, Accession NM\_131916) is another VGAM478 host target gene. PPIL3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded

by PPIL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPIL3 BINDING SITE, designated SEQ ID:28393, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22014] Another function of VGAM478 is therefore inhibition of Peptidylprolyl Isomerase (cyclophilin)-like 3 (PPIL3, Accession NM\_131916). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPIL3. LOC144962 (Accession XM\_084990) is another VGAM478 host target gene. LOC144962 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144962, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144962 BINDING SITE, designated SEQ ID:37791, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22015] Another function of VGAM478 is therefore inhibition of

LOC144962 (Accession XM\_084990). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144962. LOC150397 (Accession XM\_086907) is another VGAM478 host target gene. LOC150397 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150397 BINDING SITE, designated SEQ ID:38960, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22016] Another function of VGAM478 is therefore inhibition of LOC150397 (Accession XM\_086907). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150397. LOC152359 (Accession XM\_098213) is another VGAM478 host target gene. LOC152359 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152359, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC152359 BINDING SITE, designated SEQ ID:41493, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22017] Another function of VGAM478 is therefore inhibition of LOC152359 (Accession XM\_098213). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152359. LOC220522 (Accession XM\_018306) is another VGAM478 host target gene. LOC220522 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220522, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220522 BINDING SITE, designated SEQ ID:30351, to the nucleotide sequence of VGAM478 RNA, herein designated VGAM RNA, also designated SEQ ID:3189.

[22018] Another function of VGAM478 is therefore inhibition of LOC220522 (Accession XM\_018306). Accordingly, utilities of VGAM478 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220522. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 479 (VGAM479) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22019] VGAM479 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM479 was detected is described hereinabove with reference to Figs. 1–8.

[22020] VGAM479 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM479 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22021] VGAM479 gene encodes a VGAM479 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM479 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM479 precursor RNA is designated SEQ ID:465, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:465 is

located at position 3988 relative to the genome of Hepatitis G Virus.

[22022] VGAM479 precursor RNA folds onto itself, forming VGAM479 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22023] An enzyme complex designated DICER COMPLEX, `dices` the VGAM479 folded precursor RNA into VGAM479 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM479 RNA is designated SEQ ID:3190, and is provided hereinbelow with reference to the sequence listing part.

[22024] VGAM479 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM479 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM479 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[22025] VGAM479 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM479 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM479 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM479 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM479 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[22026] The complementary binding of VGAM479 RNA, herein designated VGAM RNA, to host target binding sites on VGAM479 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM479 host target RNA into VGAM479 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22027] It is appreciated that VGAM479 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM479 host target genes. The mRNA of each one of this plurality of VGAM479 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM479 RNA, herein designated VGAM RNA, and which when bound by VGAM479 RNA causes inhibition of translation of respective one or more VGAM479



host target proteins.

[22028] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM479 gene, herein designated VGAM GENE, on one or more VGAM479 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22029] It is yet further appreciated that a function of VGAM479 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM479 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific

functions, and accordingly utilities, of VGAM479 correlate with, and may be deduced from, the identity of the host target genes which VGAM479 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22030] Nucleotide sequences of the VGAM479 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM479 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM479 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM479 are further described hereinbelow with reference to Table 1.

[22031] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM479 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM479 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22032] As mentioned hereinabove with reference to Fig. 1, a function of VGAM479 gene, herein designated VGAM is inhibition of expression of VGAM479 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM479 correlate with, and may be deduced from, the identity of the target genes which VGAM479 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22033] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_004996) is a VGAM479 host target gene. ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABCC1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3, designated SEQ ID:11440, SEQ ID:21284 and SEQ ID:21288 respectively, to the nucleotide sequence of VGAM479 RNA, herein designated VGAM RNA, also designated SEQ ID:3190.

[22034] A function of VGAM479 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_004996), a gene which may participate directly in the active transport of drugs into sub-cellular organelles or influence drug distribution indirectly. Accordingly, utilities of VGAM479 include diagno-

sis, prevention and treatment of diseases and clinical conditions associated with ABCC1. The function of ABCC1 has been established by previous studies. Cole et al. (1992) identified a transporter protein whose gene is overexpressed in a multidrug-resistant variant of the small cell lung cancer cell line NCI-H69. Unlike most tumor cell lines that are resistant to multiple chemotherapeutic agents, it did not overexpress the transmembrane transport protein P-glycoprotein (MDR1; 171050). Cole et al. (1992) isolated cDNA clones corresponding to mRNAs overexpressed in the resistant H69 cells. One cDNA hybridized to an mRNA of 7.8 to 8.2 kb that was expressed 100- to 200-fold higher in the resistant cells than in the drug-sensitive H69 cells. Overexpression was associated with amplification of the cognate gene. The cDNA contained a single open reading frame of 1,522 amino acids encoding a protein that they designated MRP, for 'multidrug resistance-associated protein.' Database analyses demonstrated similarities in primary sequence to the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily of transport systems. Included in this superfamily are the genes for MDR1 and for the cystic fibrosis transmembrane conductance regulator (CFTR; 602421). Northern blot

analysis readily detected MRP transcripts in lung, testis, and peripheral blood mononuclear cells; MRP transcripts were below the level of detection in placenta, brain, kidney, salivary gland, uterus, liver, and spleen. By isotopic in situ hybridization, Cole et al. (1992) mapped the MRP1 gene to chromosome 16p13.1. Grant et al. (1997) located the MRP1 gene close to the short arm breakpoint of the pericentric inversion associated with the M4Eo subclass of acute myeloid leukemia and on the telomeric side of the MYH11 gene (OMIM Ref. No. 160745).

[22035] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22036] Cole, S. P. C.; Bhardwaj, G.; Gerlach, J. H.; Mackie, J. E.; Grant, C. E.; Almquist, K. C.; Stewart, A. J.; Kurz, E. U.; Duncan, A. M. V.; Deeley, R. G. : Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line. *Science* 258: 1650–1654, 1992. ; and

[22037] Grant, C. E.; Kurz, E. U.; Cole, S. P. C.; Deeley, R. G. : Analysis of the intron–exon organization of the human multidrug–resistance protein gene (MRP) and alternative splicing of its m.

[22038] Further studies establishing the function and utilities of

ABCC1 are found in John Hopkins OMIM database record ID 158343, and in cited publications numbered 2530–2536 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chemokine (C–C motif) Receptor 5 (CCR5, Accession NM\_000579) is another VGAM479 host target gene. CCR5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CCR5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CCR5 BINDING SITE, designated SEQ ID:6186, to the nucleotide sequence of VGAM479 RNA, herein designated VGAM RNA, also designated SEQ ID:3190.

[22039] Another function of VGAM479 is therefore inhibition of Chemokine (C–C motif) Receptor 5 (CCR5, Accession NM\_000579). Accordingly, utilities of VGAM479 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CCR5. KIAA1265 (Accession XM\_047707) is another VGAM479 host target gene. KIAA1265 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1265, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1265 BINDING SITE, designated SEQ ID:35035, to the nucleotide sequence of VGAM479 RNA, herein designated VGAM RNA, also designated SEQ ID:3190.

[22040] Another function of VGAM479 is therefore inhibition of KIAA1265 (Accession XM\_047707). Accordingly, utilities of VGAM479 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1265. PDZ Domain Containing 2 (PDZD2, Accession XM\_087705) is another VGAM479 host target gene. PDZD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDZD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDZD2 BINDING SITE, designated SEQ ID:39386, to the nucleotide sequence of VGAM479 RNA, herein designated VGAM RNA, also designated SEQ ID:3190.

[22041] Another function of VGAM479 is therefore inhibition of PDZ Domain Containing 2 (PDZD2, Accession

XM\_087705). Accordingly, utilities of VGAM479 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDZD2. LOC150372 (Accession XM\_086893) is another VGAM479 host target gene. LOC150372 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150372, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150372 BINDING SITE, designated SEQ ID:38943, to the nucleotide sequence of VGAM479 RNA, herein designated VGAM RNA, also designated SEQ ID:3190.

[22042] Another function of VGAM479 is therefore inhibition of LOC150372 (Accession XM\_086893). Accordingly, utilities of VGAM479 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150372. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 480 (VGAM480) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is



known in the art.

[22043] VGAM480 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM480 was detected is described hereinabove with reference to Figs. 1–8.

[22044] VGAM480 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM480 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22045] VGAM480 gene encodes a VGAM480 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM480 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM480 precursor RNA is designated SEQ ID:466, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:466 is located at position 4279 relative to the genome of Hepatitis G Virus.

[22046] VGAM480 precursor RNA folds onto itself, forming VGAM480 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[22047] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM480 folded precursor RNA into VGAM480 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 65%) nucleotide se-  
quence of VGAM480 RNA is designated SEQ ID:3191, and  
is provided hereinbelow with reference to the sequence  
listing part.

[22048] VGAM480 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM480 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM480 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[22049] VGAM480 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM480 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM480 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM480 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM480 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[22050] The complementary binding of VGAM480 RNA, herein designated VGAM RNA, to host target binding sites on VGAM480 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM480 host target RNA into VGAM480 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22051] It is appreciated that VGAM480 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM480 host target genes. The mRNA of each one of this plurality of VGAM480 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM480 RNA, herein designated VGAM RNA, and which when bound by VGAM480 RNA causes inhibition of translation of respective one or more VGAM480 host target proteins.

[22052] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM480 gene, herein designated VGAM GENE, on one or

more VGAM480 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22053] It is yet further appreciated that a function of VGAM480 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM480 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM480 correlate with, and may be deduced from, the identity of the host target genes which VGAM480 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22054] Nucleotide sequences of the VGAM480 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM480 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM480 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM480 are further described hereinbelow with reference to Table 1.

[22055] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM480 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM480 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22056] As mentioned hereinabove with reference to Fig. 1, a function of VGAM480 gene, herein designated VGAM is inhibition of expression of VGAM480 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM480 correlate with, and may be deduced from, the identity of the target genes which VGAM480 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22057] Myozenin 1 (MYOZ1, Accession NM\_021245) is a

VGAM480 host target gene. MYOZ1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MYOZ1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYOZ1 BINDING SITE, designated SEQ ID:22213, to the nucleotide sequence of VGAM480 RNA, herein designated VGAM RNA, also designated SEQ ID:3191.

[22058] A function of VGAM480 is therefore inhibition of Myozenin 1 (MYOZ1, Accession NM\_021245), a gene which modulates the function and substrate specificity of calcineurin in striated muscle cells. Accordingly, utilities of VGAM480 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYOZ1. The function of MYOZ1 has been established by previous studies. Calcineurin (see OMIM Ref. No. 114105) is a calcium/calmodulin-dependent serine-threonine phosphatase that plays an important role in transducing calcium-dependent signals in a variety of cell types. Calcineurin has also been shown to have a profound influence on the properties of striated muscle cells, including cardiac muscle. To identify potential cardiac-specific reg-

ulators of calcineurin, Frey et al. (2000) conducted a yeast 2-hybrid screen, using the catalytic A subunit of calcineurin as bait. They identified a novel family of striated muscle-specific calcineurin-interacting proteins called calsarcins. Calsarcins interact and colocalize with the Z-disc protein alpha-actinin (ACTN1; 102575) in vitro and in vivo and thereby tether calcineurin to the sarcomere of cardiac and skeletal muscle. These properties of calsarcins suggest an important role for these proteins in modulating the function and substrate specificity of calcineurin in striated muscle cells. Using the yeast 2-hybrid system, Takada et al. (2001) used sarcomeric isoforms of alpha-actinin and gamma-filamin to screen a human skeletal muscle cDNA library for interacting proteins. The aim was to understand better the structure and function of Z lines. They described the characteristics of myozenin. It is predicted to be a 32-kD globular protein with a central glycine-rich domain flanked by alpha-helical regions with no strong homologies to any known genes. The MYOZ gene has 6 exons and maps to chromosome 10q22.1-q22.2; a homologous EST in the public database had been mapped to 10q22.1 by radiation hybrid mapping. Takada et al. (2001) considered myozenin as a



skeletal muscle Z-line protein to be a candidate gene for limb-girdle muscular dystrophy or other neuromuscular disorders.

[22059] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22060] Frey, N.; Richardson, J. A.; Olson, E. N. : Calsarcins, a novel family of sarcomeric calcineurin-binding proteins. Proc. Nat. Acad. Sci. 97: 14632-14637, 2000. ; and

[22061] Takada, F.; Vander Woude, D. L.; Tong, H.-Q.; Thompson, T. G.; Watkins, S. C.; Kunkel, L. M.; Beggs, A. H. : Myozenin: an alpha-actinin- and gamma-filamin-binding protein of skeletal m.

[22062] Further studies establishing the function and utilities of MYOZ1 are found in John Hopkins OMIM database record ID 605603, and in cited publications numbered 700 and 7004 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Baculoviral IAP Repeat-containing 8 (BIRC8, Accession NM\_033341) is another VGAM480 host target gene. BIRC8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BIRC8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BIRC8 BINDING SITE, designated SEQ ID:27195, to the nucleotide sequence of VGAM480 RNA, herein designated VGAM RNA, also designated SEQ ID:3191.

[22063] Another function of VGAM480 is therefore inhibition of Baculoviral IAP Repeat-containing 8 (BIRC8, Accession NM\_033341). Accordingly, utilities of VGAM480 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BIRC8. DKFZp762M136 (Accession XM\_035635) is another VGAM480 host target gene. DKFZp762M136 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp762M136, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762M136 BINDING SITE, designated SEQ ID:32301, to the nucleotide sequence of VGAM480 RNA, herein designated VGAM RNA, also designated SEQ ID:3191.

[22064] Another function of VGAM480 is therefore inhibition of DKFZp762M136 (Accession XM\_035635). Accordingly, utilities of VGAM480 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with DKFZp762M136. FLJ20449 (Accession NM\_017826) is another VGAM480 host target gene. FLJ20449 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20449, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20449 BINDING SITE, designated SEQ ID:19485, to the nucleotide sequence of VGAM480 RNA, herein designated VGAM RNA, also designated SEQ ID:3191.

[22065] Another function of VGAM480 is therefore inhibition of FLJ20449 (Accession NM\_017826). Accordingly, utilities of VGAM480 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20449. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 481 (VGAM481) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22066] VGAM481 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM481 was detected is described hereinabove with reference to Figs. 1–8.

[22067] VGAM481 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus.

VGAM481 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22068] VGAM481 gene encodes a VGAM481 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM481 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM481 precursor RNA is designated SEQ ID:467, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:467 is located at position 2786 relative to the genome of Hepatitis G Virus.

[22069] VGAM481 precursor RNA folds onto itself, forming VGAM481 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22070] An enzyme complex designated DICER COMPLEX, `dices` the VGAM481 folded precursor RNA into VGAM481 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 83%) nucleotide sequence of VGAM481 RNA is designated SEQ ID:3192, and is provided hereinbelow with reference to the sequence listing part.

[22071] VGAM481 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM481 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM481 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22072] VGAM481 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM481 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM481 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM481 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM481 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22073] The complementary binding of VGAM481 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM481 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM481 host target RNA into VGAM481 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22074] It is appreciated that VGAM481 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM481 host target genes. The mRNA of each one of this plurality of VGAM481 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM481 RNA, herein designated VGAM RNA, and which when bound by VGAM481 RNA causes inhibition of translation of respective one or more VGAM481 host target proteins.

[22075] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM481 gene, herein designated VGAM GENE, on one or more VGAM481 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22076] It is yet further appreciated that a function of VGAM481 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM481 correlate with, and may be deduced from, the identity of the host target genes which VGAM481 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22077] Nucleotide sequences of the VGAM481 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM481 RNA, herein designated VGAM RNA,



and a schematic representation of the secondary folding of VGAM481 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM481 are further described hereinbelow with reference to Table 1.

[22078] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM481 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM481 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22079] As mentioned hereinabove with reference to Fig. 1, a function of VGAM481 gene, herein designated VGAM is inhibition of expression of VGAM481 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM481 correlate with, and may be deduced from, the identity of the target genes which VGAM481 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22080] Adenylate Cyclase 7 (ADCY7, Accession NM\_001114) is a VGAM481 host target gene. ADCY7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADCY7, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADCY7 BINDING SITE, designated SEQ ID:6785, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22081] A function of VGAM481 is therefore inhibition of Adenylate Cyclase 7 (ADCY7, Accession NM\_001114), a gene which is a membrane-bound,  $Ca^{2+}$ -inhibitable adenylyl cyclase. Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADCY7. The function of ADCY7 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM108.BTB and CNC Homology 1, Basic Leucine Zipper Transcription Factor 2 (BACH2, Accession NM\_021813) is another VGAM481 host target gene. BACH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BACH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACH2 BINDING SITE,

designated SEQ ID:22380, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22082] Another function of VGAM481 is therefore inhibition of BTB and CNC Homology 1, Basic Leucine Zipper Transcription Factor 2 (BACH2, Accession NM\_021813), a gene which acts as repressor or activator, binds to maf recognition elements. Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACH2. The function of BACH2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM331.B-cell CLL/lymphoma 6 (zinc finger protein 51) (BCL6, Accession NM\_001706) is another VGAM481 host target gene. BCL6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BCL6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL6 BINDING SITE, designated SEQ ID:7430, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22083] Another function of VGAM481 is therefore inhibition of B-cell CLL/lymphoma 6 (zinc finger protein 51) (BCL6, Accession NM\_001706), a gene which is involved in the generation and maintenance of both T and B cells during immune responses. Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL6. The function of BCL6 has been established by previous studies. Chromosomal translocations involving chromosome 3q27 and immunoglobulin gene regions are among the most common rearrangements in B-cell non-Hodgkin lymphoma. Using a probe from the immunoglobulin heavy chain joining region locus (OMIM Ref. No. 147010), Baron et al. (1993) isolated genomic clones from a bacteriophage lambda library prepared from a lymphoma characterized by a translocation t(3;14)(q27;q32). Normal chromosome 3 sequences and the reciprocal breakpoint junction were isolated. DNA probes on each side of the chromosome 3 breakpoint hybridized at high stringency to the DNA of various mammalian species, demonstrating evolutionary conservation. A probe made from partial cDNA clones isolated from a T-cell line hybridized the genomic DNA from both sides of the chromosome 3 breakpoint, indicating

that the t(3;14) is associated with a break within the gene on chromosome 3. In situ chromosomal hybridization revealed that the same gene is involved in the t(3;22)(q27;q11). Preliminary nucleotide sequencing showed no identity of the cDNA to gene sequences in available data banks. Baron et al. (1993) proposed the name B-cell lymphoma-6 (BCL6) for this gene, which they presumed plays a role in the pathogenesis of certain B-cell lymphomas. Ye et al. (1993) cloned the BCL6 gene. Animal model experiments lend further support to the function of BCL6. Ichii et al. (2002) observed that the percentage of CD8 (see OMIM Ref. No. 186910)-positive T cells with a memory phenotype was lower in Bcl6 -/- mice than in wildtype mice, while the percentage of activated T cells was the same. Transgenic mice and 'rescued' Bcl6 -/- mice expressing the Bcl6 transgene specifically in T cells had levels of memory CD8 cells like those of wildtype mice. After antigenic stimulation, memory CD8 cells, which express CD44 (OMIM Ref. No. 107269), Ly6C (see OMIM Ref. No. LY6D; 606204), CD122 (OMIM Ref. No. 146710), and Bcl2 (OMIM Ref. No. 151430), differentiated into effector cells more rapidly than nonmemory CD8 cells in wildtype mice. Analysis of CD8-positive T-cell prolifer-

ation indicated that memory-type CD8 cells proliferated through a homeostatic mechanism in a Bcl6-dependent manner in the lymphopenic environment of very young mouse spleens. Ichii et al. (2002) concluded that BCL6 is involved in the generation and maintenance of both T and B cells during immune responses.

[22084] It is appreciated that the abovementioned animal model for BCL6 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[22085] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22086] Ye, B. H.; Rao, P. H.; Chaganti, R. S. K.; Dalla-Favera, R. : Cloning of bcl-6, the locus involved in chromosome translocations affecting band 3q27 in B-cell lymphoma. Cancer Res. 53: 2732-2735, 1993. ; and

[22087] Ichii, H.; Sakamoto, A.; Hatano, M.; Okada, S.; Toyama, H.; Taki, S.; Arima, M.; Kuroda, Y.; Tokuhisa, T. : Role of Bcl-6 in the generation and maintenance of memory CD8+ T cells. Natu.

[22088] Further studies establishing the function and utilities of BCL6 are found in John Hopkins OMIM database record ID

109565, and in cited publications numbered 1362–1371, 607, 1372–1378, 45 and 1379–1386 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Heterogeneous Nuclear Ribonucleoprotein F (HNRPF, Accession NM\_004966) is another VGAM481 host target gene. HNRPF BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by HNRPF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HNRPF BINDING SITE, designated SEQ ID:11415, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22089] Another function of VGAM481 is therefore inhibition of Heterogeneous Nuclear Ribonucleoprotein F (HNRPF, Accession NM\_004966). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HNRPF. Inositol Hexaphosphate Kinase 3 (IHPK3, Accession NM\_054111) is another VGAM481 host target gene. IHPK3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by IHPK3, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IHPK3 BINDING SITE, designated SEQ ID:27658, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22090] Another function of VGAM481 is therefore inhibition of Inositol Hexaphosphate Kinase 3 (IHPK3, Accession NM\_054111). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IHPK3. Neuron Navigator 2 (NAV2, Accession XM\_012028) is another VGAM481 host target gene. NAV2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NAV2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAV2 BINDING SITE, designated SEQ ID:30205, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22091] Another function of VGAM481 is therefore inhibition of Neuron Navigator 2 (NAV2, Accession XM\_012028), a



gene which plays an important role in neuronal development, including neurite outgrowth. Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAV2. The function of NAV2 has been established by previous studies. The vitamin A metabolite, all-trans retinoic acid (atRA), plays an important role in neuronal development, including neurite outgrowth. RAINB1 is an atRA-responsive gene.

[22092] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22093] Merrill, R. A.; Plum, L. A.; Kaiser, M. E.; Clagett-Dame, M. : A mammalian homolog of unc-53 is regulated by all-trans retinoic acid in neuroblastoma cells and embryos. Proc. Nat. Acad. Sci. 99: 3422-3427, 2002. ; and

[22094] Nagase, T.; Kikuno, R.; Ishikawa, K.; Hirose, M.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. XVI. The complete sequences of 150 new cDNA clones from.

[22095] Further studies establishing the function and utilities of NAV2 are found in John Hopkins OMIM database record ID 607026, and in cited publications numbered 538 and

6371 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. NKX3A (Accession NM\_006167) is another VGAM481 host target gene. NKX3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NKX3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NKX3A BINDING SITE, designated SEQ ID:12826, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22096] Another function of VGAM481 is therefore inhibition of NKX3A (Accession NM\_006167), a gene which may regulate gene expression and control cell differentiation. Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NKX3A. The function of NKX3A has been established by previous studies. Using a random cDNA sequencing approach, He et al. (1997) cloned a novel prostate-specific gene that encodes a homeo box-containing protein. The gene, which they symbolized NKX3.1, encodes a deduced 234-amino acid polypeptide

with greatest homology to the *Drosophila* NK3 gene. Northern blot analysis showed that NKX3.1 had a uniquely restricted tissue expression pattern. The 3.5-kb NKX3.1 mRNA was abundant in the prostate, present at a lower level in the testis, and absent from all other tissues tested. He et al. (1997) detected NKX3.1 expression in a hormone-responsive, androgen receptor-positive prostate cancer cell line, but not in either of 2 androgen receptor-negative prostate cancer cell lines, or in 11 other cell lines of varied origin. Androgen stimulation markedly increased NKX3.1 expression in an androgen-dependent carcinoma line. The authors suggested that the NKX3.1 gene plays a role in androgen-driven differentiation of prostatic tissue and in the loss of that differentiation during the progression of prostate cancer. Animal model experiments lend further support to the function of NKX3A. Abdulkadir et al. (2002) found that conditional deletion of one or both alleles of *Nkx3.1* in transgenic mice led to the development of preinvasive lesions resembling human prostatic intraepithelial neoplasia.

[22097] It is appreciated that the abovementioned animal model for NKX3A is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appre-

ciated from the publications sited hereinbelow.

[22098] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22099] Abdulkadir, S. A.; Magee, J. A.; Peters, T. J.; Kaleem, Z.; Naughton, C. K.; Humphrey, P. A.; Milbrandt, J. : Conditional loss of Nkx3.1 in adult mice induces prostatic intraepithelial neoplasia. *Molec. Cell. Biol.* 22: 1495–1503, 2002. ; and

[22100] He, W. W.; Sciavolino, P. J.; Wing, J.; Augustus, M.; Hudson, P.; Meissner, P. S.; Curtis, R. T.; Shell, B. K.; Bostwick, D. G.; Tindall, D. J.; Gelmann, E. P.; Abate-Shen, C.; Carter.

[22101] Further studies establishing the function and utilities of NKX3A are found in John Hopkins OMIM database record ID 602041, and in sited publications numbered 6656–665 and 6659 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromobox Homolog 6 (CBX6, Accession NM\_014292) is another VGAM481 host target gene. CBX6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CBX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus–

trates the complementarity of the nucleotide sequences of CBX6 BINDING SITE, designated SEQ ID:15576, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22102] Another function of VGAM481 is therefore inhibition of Chromobox Homolog 6 (CBX6, Accession NM\_014292). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBX6. Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665) is another VGAM481 host target gene. EVI5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EVI5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVI5 BINDING SITE, designated SEQ ID:12207, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22103] Another function of VGAM481 is therefore inhibition of Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with EVI5. FLJ20967 (Accession NM\_022071) is another VGAM481 host target gene. FLJ20967 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20967, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20967 BINDING SITE, designated SEQ ID:22615, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22104] Another function of VGAM481 is therefore inhibition of FLJ20967 (Accession NM\_022071). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20967. FLJ31978 (Accession NM\_144669) is another VGAM481 host target gene. FLJ31978 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ31978, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ31978 BINDING SITE, designated SEQ ID:29489, to the nucleotide sequence of

VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22105] Another function of VGAM481 is therefore inhibition of FLJ31978 (Accession NM\_144669). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ31978. KIAA0960 (Accession XM\_166543) is another VGAM481 host target gene. KIAA0960 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0960, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0960 BINDING SITE, designated SEQ ID:44518, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22106] Another function of VGAM481 is therefore inhibition of KIAA0960 (Accession XM\_166543). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0960. MGC35521 (Accession NM\_145065) is another VGAM481 host target gene. MGC35521 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by MGC35521, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC35521 BINDING SITE, designated SEQ ID:29703, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22107] Another function of VGAM481 is therefore inhibition of MGC35521 (Accession NM\_145065). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC35521. RASD Family, Member 2 (RASD2, Accession NM\_014310) is another VGAM481 host target gene. RASD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RASD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASD2 BINDING SITE, designated SEQ ID:15606, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22108] Another function of VGAM481 is therefore inhibition of



RASD Family, Member 2 (RASD2, Accession NM\_014310). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASD2. LOC126432 (Accession XM\_059046) is another VGAM481 host target gene. LOC126432 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC126432, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126432 BINDING SITE, designated SEQ ID:36841, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22109] Another function of VGAM481 is therefore inhibition of LOC126432 (Accession XM\_059046). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126432. LOC144866 (Accession XM\_096699) is another VGAM481 host target gene. LOC144866 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC144866, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144866 BINDING SITE, designated SEQ ID:40475, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22110] Another function of VGAM481 is therefore inhibition of LOC144866 (Accession XM\_096699). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144866. LOC146316 (Accession XM\_027568) is another VGAM481 host target gene. LOC146316 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146316 BINDING SITE, designated SEQ ID:30525, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22111] Another function of VGAM481 is therefore inhibition of LOC146316 (Accession XM\_027568). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC146316. LOC150481 (Accession XM\_086929) is another VGAM481 host target gene. LOC150481 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150481, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150481 BINDING SITE, designated SEQ ID:38981, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22112] Another function of VGAM481 is therefore inhibition of LOC150481 (Accession XM\_086929). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150481. LOC64744 (Accession XM\_029830) is another VGAM481 host target gene. LOC64744 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC64744, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC64744 BINDING SITE, designated SEQ ID:30951, to the nucleotide sequence of VGAM481 RNA, herein designated

VGAM RNA, also designated SEQ ID:3192.

[22113] Another function of VGAM481 is therefore inhibition of LOC64744 (Accession XM\_029830). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC64744. LOC91266 (Accession XM\_037268) is another VGAM481 host target gene. LOC91266 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91266, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91266 BINDING SITE, designated SEQ ID:32602, to the nucleotide sequence of VGAM481 RNA, herein designated VGAM RNA, also designated SEQ ID:3192.

[22114] Another function of VGAM481 is therefore inhibition of LOC91266 (Accession XM\_037268). Accordingly, utilities of VGAM481 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91266. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 482 (VGAM482) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22115] VGAM482 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM482 was detected is described hereinabove with reference to Figs. 1–8.

[22116] VGAM482 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM482 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22117] VGAM482 gene encodes a VGAM482 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM482 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM482 precursor RNA is designated SEQ ID:468, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:468 is located at position 2953 relative to the genome of Hepatitis G Virus.

[22118] VGAM482 precursor RNA folds onto itself, forming

VGAM482 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22119] An enzyme complex designated DICER COMPLEX, `dices` the VGAM482 folded precursor RNA into VGAM482 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 60%) nucleotide sequence of VGAM482 RNA is designated SEQ ID:3193, and is provided hereinbelow with reference to the sequence listing part.

[22120] VGAM482 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM482 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM482 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22121] VGAM482 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM482 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM482 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM482 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM482 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22122] The complementary binding of VGAM482 RNA, herein designated VGAM RNA, to host target binding sites on VGAM482 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM482 host target RNA into VGAM482 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22123] It is appreciated that VGAM482 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM482 host target genes. The mRNA of each one of this plurality of VGAM482 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM482 RNA, herein designated VGAM RNA, and which when bound by VGAM482 RNA causes inhibition of translation of respective one or more VGAM482 host target proteins.

[22124] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with



specific reference to translational inhibition exerted by VGAM482 gene, herein designated VGAM GENE, on one or more VGAM482 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22125] It is yet further appreciated that a function of VGAM482 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM482 correlate with, and may be deduced from, the identity of the host target genes which VGAM482 binds and inhibits, and the

function of these host target genes, as elaborated herein–below.

[22126] Nucleotide sequences of the VGAM482 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM482 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM482 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM482 are further described hereinbelow with reference to Table 1.

[22127] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM482 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM482 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22128] As mentioned hereinabove with reference to Fig. 1, a function of VGAM482 gene, herein designated VGAM is inhibition of expression of VGAM482 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM482 correlate with, and may be deduced from, the identity of the target genes which VGAM482 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[22129] Chromosome 1 Open Reading Frame 1 (C1orf1, Accession NM\_001213) is a VGAM482 host target gene. C1orf1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C1orf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1orf1 BINDING SITE, designated SEQ ID:6874, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22130] A function of VGAM482 is therefore inhibition of Chromosome 1 Open Reading Frame 1 (C1orf1, Accession NM\_001213). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf1. CSE1 Chromosome Segregation 1-like (yeast) (CSE1L, Accession XM\_030044) is another VGAM482 host target gene. CSE1L BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CSE1L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

CSE1L BINDING SITE, designated SEQ ID:30990, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22131] Another function of VGAM482 is therefore inhibition of CSE1 Chromosome Segregation 1-like (yeast) (CSE1L, Accession XM\_030044). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSE1L. Gap Junction Protein, Beta 3, 31kDa (connexin 31) (GJB3, Accession NM\_024009) is another VGAM482 host target gene. GJB3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GJB3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GJB3 BINDING SITE, designated SEQ ID:23441, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22132] Another function of VGAM482 is therefore inhibition of Gap Junction Protein, Beta 3, 31kDa (connexin 31) (GJB3, Accession NM\_024009). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GJB3. Protein Ki-

nase, Lysine Deficient 3 (PRKWNK3, Accession XM\_029183) is another VGAM482 host target gene. PRKWNK3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PRKWNK3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKWNK3 BINDING SITE, designated SEQ ID:30855, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22133] Another function of VGAM482 is therefore inhibition of Protein Kinase, Lysine Deficient 3 (PRKWNK3, Accession XM\_029183). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKWNK3. RNA (guanine-7-) Methyltransferase (RNMT, Accession NM\_003799) is another VGAM482 host target gene. RNMT BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RNMT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

RNMT BINDING SITE, designated SEQ ID:9878, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22134] Another function of VGAM482 is therefore inhibition of RNA (guanine-7-) Methyltransferase (RNMT, Accession NM\_003799), a gene which catalyzes the methylation of GpppN- at the guanine N7 position. Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNMT. The function of RNMT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178. Chromosome 20 Open Reading Frame 126 (C20orf126, Accession NM\_030815) is another VGAM482 host target gene. C20orf126 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf126, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf126 BINDING SITE, designated SEQ ID:25134, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22135] Another function of VGAM482 is therefore inhibition of Chromosome 20 Open Reading Frame 126 (C20orf126, Accession NM\_030815). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf126.

FLJ12987 (Accession NM\_025170) is another VGAM482 host target gene. FLJ12987 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12987, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12987 BINDING SITE, designated SEQ ID:24807, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22136] Another function of VGAM482 is therefore inhibition of FLJ12987 (Accession NM\_025170). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12987. PR Domain Containing 8 (PRDM8, Accession NM\_020226) is another VGAM482 host target gene. PRDM8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRDM8, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRDM8 BINDING SITE, designated SEQ ID:21490, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22137] Another function of VGAM482 is therefore inhibition of PR Domain Containing 8 (PRDM8, Accession NM\_020226). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRDM8. Sema Domain, Seven Thrombospondin Repeats (type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM\_003966) is another VGAM482 host target gene. SEMA5A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SEMA5A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA5A BINDING SITE, designated SEQ ID:10103, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.



[22138] Another function of VGAM482 is therefore inhibition of Sema Domain, Seven Thrombospondin Repeats (type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM\_003966). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA5A. TU12B1-TY (Accession NM\_016575) is another VGAM482 host target gene. TU12B1-TY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TU12B1-TY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TU12B1-TY BINDING SITE, designated SEQ ID:18644, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22139] Another function of VGAM482 is therefore inhibition of TU12B1-TY (Accession NM\_016575). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TU12B1-TY. LOC167040 (Accession XM\_106497) is another VGAM482 host target gene. LOC167040 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC167040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC167040 BINDING SITE, designated SEQ ID:42202, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22140] Another function of VGAM482 is therefore inhibition of LOC167040 (Accession XM\_106497). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC167040. LOC91050 (Accession XM\_035703) is another VGAM482 host target gene. LOC91050 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC91050, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91050 BINDING SITE, designated SEQ ID:32340, to the nucleotide sequence of VGAM482 RNA, herein designated VGAM RNA, also designated SEQ ID:3193.

[22141] Another function of VGAM482 is therefore inhibition of

LOC91050 (Accession XM\_035703). Accordingly, utilities of VGAM482 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91050. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 483 (VGAM483) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22142] VGAM483 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM483 was detected is described hereinabove with reference to Figs. 1–8.

[22143] VGAM483 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM483 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22144] VGAM483 gene encodes a VGAM483 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM483 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM483 precursor RNA is designated SEQ ID:469, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:469 is located at position 4804 relative to the genome of Hepatitis G Virus.

[22145] VGAM483 precursor RNA folds onto itself, forming VGAM483 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22146] An enzyme complex designated DICER COMPLEX, `dices` the VGAM483 folded precursor RNA into VGAM483 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 67%) nucleotide se-

quence of VGAM483 RNA is designated SEQ ID:3194, and is provided hereinbelow with reference to the sequence listing part.

[22147] VGAM483 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM483 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM483 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[22148] VGAM483 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM483 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM483 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM483 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM483 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22149] The complementary binding of VGAM483 RNA, herein designated VGAM RNA, to host target binding sites on VGAM483 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM483 host target RNA into VGAM483 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22150] It is appreciated that VGAM483 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM483 host target genes. The mRNA of each one of this plurality of VGAM483 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM483 RNA, herein designated VGAM RNA, and which when bound by VGAM483 RNA causes inhibition of translation of respective one or more VGAM483 host target proteins.

[22151] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM483 gene, herein designated VGAM GENE, on one or more VGAM483 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22152] It is yet further appreciated that a function of VGAM483 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM483 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM483 correlate with, and may be deduced from, the identity of the host target genes which VGAM483 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22153] Nucleotide sequences of the VGAM483 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM483 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM483 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM483 are further described hereinbelow with reference to Table 1.

[22154] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM483 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM483 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.



[22155] As mentioned hereinabove with reference to Fig. 1, a function of VGAM483 gene, herein designated VGAM is inhibition of expression of VGAM483 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM483 correlate with, and may be deduced from, the identity of the target genes which VGAM483 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22156] N-ethylmaleimide-sensitive Factor Attachment Protein, Gamma (NAPG, Accession XM\_172983) is a VGAM483 host target gene. NAPG BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NAPG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAPG BINDING SITE, designated SEQ ID:46249, to the nucleotide sequence of VGAM483 RNA, herein designated VGAM RNA, also designated SEQ ID:3194.

[22157] A function of VGAM483 is therefore inhibition of N-ethylmaleimide-sensitive Factor Attachment Protein, Gamma (NAPG, Accession XM\_172983). Accordingly, utilities of VGAM483 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with NAPG. LOC196955 (Accession XM\_085210) is another VGAM483 host target gene. LOC196955 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196955, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196955 BINDING SITE, designated SEQ ID:37925, to the nucleotide sequence of VGAM483 RNA, herein designated VGAM RNA, also designated SEQ ID:3194.

[22158] Another function of VGAM483 is therefore inhibition of LOC196955 (Accession XM\_085210). Accordingly, utilities of VGAM483 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196955. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 484 (VGAM484) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22159] VGAM484 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM484 was detected is described hereinabove with reference to Figs. 1–8.

[22160] VGAM484 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus.

VGAM484 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22161] VGAM484 gene encodes a VGAM484 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM484 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM484 precursor RNA is designated SEQ ID:470, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:470 is located at position 6210 relative to the genome of Hepatitis G Virus.

[22162] VGAM484 precursor RNA folds onto itself, forming VGAM484 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22163] An enzyme complex designated DICER COMPLEX, `dices` the VGAM484 folded precursor RNA into VGAM484 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM484 RNA is designated SEQ ID:3195, and is provided hereinbelow with reference to the sequence listing part.

[22164] VGAM484 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM484 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM484 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22165] VGAM484 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM484 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM484 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM484 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM484 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22166] The complementary binding of VGAM484 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM484 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM484 host target RNA into VGAM484 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22167] It is appreciated that VGAM484 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM484 host target genes. The mRNA of each one of this plurality of VGAM484 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM484 RNA, herein designated VGAM RNA, and which when bound by VGAM484 RNA causes inhibition of translation of respective one or more VGAM484 host target proteins.

[22168] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM484 gene, herein designated VGAM GENE, on one or more VGAM484 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22169] It is yet further appreciated that a function of VGAM484 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM484 correlate with, and may be deduced from, the identity of the host target genes which VGAM484 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22170] Nucleotide sequences of the VGAM484 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM484 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM484 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM484 are further described hereinbelow with reference to Table 1.

[22171] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM484 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM484 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22172] As mentioned hereinabove with reference to Fig. 1, a function of VGAM484 gene, herein designated VGAM is inhibition of expression of VGAM484 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM484 correlate with, and may be deduced from, the identity of the target genes which VGAM484 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22173] Complement Component 5 Receptor 1 (C5a ligand) (C5R1, Accession NM\_001736) is a VGAM484 host target gene. C5R1 BINDING SITE is HOST TARGET binding site found in



the 3' untranslated region of mRNA encoded by C5R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C5R1 BINDING SITE, designated SEQ ID:7473, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22174] A function of VGAM484 is therefore inhibition of Complement Component 5 Receptor 1 (C5a ligand) (C5R1, Accession NM\_001736), a gene which has a nonredundant function and is required for mucosal host cell defense in the lung. Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C5R1. The function of C5R1 has been established by previous studies. Using a panel of somatic cell hybrids, Bao et al. (1992) mapped the receptor for the chemotactic ligand C5a to chromosome 19. This receptor, like those for the formyl peptides (136537, 136538) and interleukin-8 (OMIM Ref. No. 146929), is structurally related to rhodopsin (RHO; 180380) and transduces signals via intracellular GTP-binding proteins. Additionally, this receptor is similar to chemokine receptor-like 1 (OMIM Ref. No. 601531). Hopken et al. (1996)

deleted the murine C5a receptor (C5ar) through homologous recombination. They reported that the C5ar-deficient mice showed no developmental or biologic defects in cells in which C5a is expressed (e.g., myeloid cell lineages, hepatocytes, and epithelial cells) apart from the ability to bind and signal to exogenous C5a. Hopken et al. (1996) reported that C5ar-deficient mice bred normally and displayed no gross defects when maintained under barrier conditions. When mice were challenged with intratracheal *Pseudomonas aeruginosa*, the C5ar-deficient mice, in contrast to their littermates, were unable to clear the bacteria and they succumbed to pneumonia. On the basis of these studies, Hopken et al. (1996) concluded that C5ar has a nonredundant function and is required for mucosal host cell defense in the lung.

[22175] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22176] Hopken, U. E.; Lu, D.; Gerard, N. P.; Gerard, C. : The C5a chemoattractant receptor mediates mucosal defense to infection. *Nature* 383: 86–89, 1996. ; and

[22177] Bao, L.; Gerard, N. P.; Eddy, R. L., Jr.; Shows, T. B.; Gerard, C. : Mapping of genes for the human C5a receptor (C5AR),

human FMLP receptor (FPR), and two FMLP receptor homologue orphan.

[22178] Further studies establishing the function and utilities of C5R1 are found in John Hopkins OMIM database record ID 113995, and in cited publications numbered 2131, 3731–3732, 4555–373 and 4225 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cytoplasmic Linker 2 (CYLN2, Accession NM\_003388) is another VGAM484 host target gene. CYLN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYLN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYLN2 BINDING SITE, designated SEQ ID:9423, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22179] Another function of VGAM484 is therefore inhibition of Cytoplasmic Linker 2 (CYLN2, Accession NM\_003388), a gene which associates with microtubules and dendritic lamellar bodies. Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with CYLN2. The function of CYLN2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM94.DXS1283E (Accession XM\_047871) is another VGAM484 host target gene. DXS1283E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DXS1283E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DXS1283E BINDING SITE, designated SEQ ID:35065, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22180] Another function of VGAM484 is therefore inhibition of DXS1283E (Accession XM\_047871). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DXS1283E. Ribonuclease/angiogenin Inhibitor (RNH, Accession NM\_002939) is another VGAM484 host target gene. RNH BINDING SITE1 and RNH BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RNH, corresponding to HOST TAR-

GET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNH BINDING SITE1 and RNH BINDING SITE2, designated SEQ ID:8845 and SEQ ID:29994 respectively, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22181] Another function of VGAM484 is therefore inhibition of Ribonuclease/angiogenin Inhibitor (RNH, Accession NM\_002939), a gene which is an inhibitor of pancreatic rnaase and angiogenin. may also function in the modulation of cellular activities. Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNH. The function of RNH has been established by previous studies. Placental ribonuclease inhibitor is a member of a family of proteinaceous cytoplasmic RNase inhibitors that occur in many tissues and bind to both intracellular and extracellular RNases. In addition to control of intracellular RNases, the inhibitor may have a role in the regulation of angiogenin (OMIM Ref. No. 105850). Ribonuclease inhibitor, of 50,000 Da, binds to ribonucleases and holds them in a latent form. Since neutral and alkaline ribonucleases proba-

bly play a critical role in the turnover of RNA in eukaryotic cells, RNH may be essential for control of mRNA turnover; the interaction of eukaryotic cells with ribonuclease may be reversible in vivo. Lee et al. (1988) determined the primary structure of PRI from the cDNA. The mature protein encodes a 460-amino acid polypeptide with a molecular mass of 49,847 kD. The amino acid sequence contains 7 direct internal repeat units, each 57 amino acids in length. These repeat units comprise 87% of the molecule. The average degree of identity between any 2 is 39%. By study of human-rodent somatic cell hybrids and by in situ hybridization, Weremowicz et al. (1990) mapped the PRI gene to 11p15. The localization was further refined to 11p15.5, distal to the IGF2 gene, by in situ hybridization to metaphase chromosomes from a cell line with a well-characterized translocation involving a breakpoint between IGF2 (OMIM Ref. No. 147470) and HRAS (OMIM Ref. No. 190020). Zneimer et al. (1990) localized the RNH gene to 11p15.5 by in situ hybridization

[22182] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22183] Weremowicz, S.; Fox, E. A.; Morton, C. C.; Vallee, B. L. :

The placental ribonuclease inhibitor (RNH) gene is located on chromosome subband 11p15.5. Genomics 8: 717–721, 1990. ; and

[22184] Zneimer, S. M.; Crawford, D.; Schneider, N. R.; Beutler, B. : Mapping of the human ribonuclease inhibitor gene (RNH) to chromosome 11p15 by in situ hybridization. Genomics 8: 175–178, 19.

[22185] Further studies establishing the function and utilities of RNH are found in John Hopkins OMIM database record ID 173320, and in cited publications numbered 9830–9832 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. EDR2 (Accession XM\_018136) is another VGAM484 host target gene. EDR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EDR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EDR2 BINDING SITE, designated SEQ ID:30337, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22186] Another function of VGAM484 is therefore inhibition of EDR2 (Accession XM\_018136). Accordingly, utilities of

VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EDR2.

FLJ14800 (Accession NM\_032840) is another VGAM484 host target gene. FLJ14800 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14800, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14800 BINDING SITE, designated SEQ ID:26621, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22187] Another function of VGAM484 is therefore inhibition of FLJ14800 (Accession NM\_032840). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14800. FLJ23342 (Accession NM\_024631) is another VGAM484 host target gene. FLJ23342 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23342, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23342 BINDING SITE,



designated SEQ ID:23897, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22188] Another function of VGAM484 is therefore inhibition of FLJ23342 (Accession NM\_024631). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23342. FLJ23519 (Accession NM\_032240) is another VGAM484 host target gene. FLJ23519 BINDING SITE1 and FLJ23519 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ23519, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23519 BINDING SITE1 and FLJ23519 BINDING SITE2, designated SEQ ID:25975 and SEQ ID:34308 respectively, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22189] Another function of VGAM484 is therefore inhibition of FLJ23519 (Accession NM\_032240). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23519. KIAA0607 (Accession XM\_051931) is another VGAM484

host target gene. KIAA0607 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0607, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0607 BINDING SITE, designated SEQ ID:35925, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22190] Another function of VGAM484 is therefore inhibition of KIAA0607 (Accession XM\_051931). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0607. KIAA0674 (Accession XM\_027054) is another VGAM484 host target gene. KIAA0674 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0674, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0674 BINDING SITE, designated SEQ ID:30398, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22191] Another function of VGAM484 is therefore inhibition of KIAA0674 (Accession XM\_027054). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0674. KIAA1473 (Accession XM\_047550) is another VGAM484 host target gene. KIAA1473 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1473, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1473 BINDING SITE, designated SEQ ID:34996, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22192] Another function of VGAM484 is therefore inhibition of KIAA1473 (Accession XM\_047550). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1473. P450RAI-2 (Accession NM\_019885) is another VGAM484 host target gene. P450RAI-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P450RAI-2, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P450RAI-2 BINDING SITE, designated SEQ ID:21267, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22193] Another function of VGAM484 is therefore inhibition of P450RAI-2 (Accession NM\_019885). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P450RAI-2. LOC112868 (Accession XM\_053402) is another VGAM484 host target gene. LOC112868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC112868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112868 BINDING SITE, designated SEQ ID:36078, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22194] Another function of VGAM484 is therefore inhibition of LOC112868 (Accession XM\_053402). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC112868. LOC51644 (Accession NM\_016057) is another VGAM484 host target gene. LOC51644 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51644, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51644 BINDING SITE, designated SEQ ID:18131, to the nucleotide sequence of VGAM484 RNA, herein designated VGAM RNA, also designated SEQ ID:3195.

[22195] Another function of VGAM484 is therefore inhibition of LOC51644 (Accession NM\_016057). Accordingly, utilities of VGAM484 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51644. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 485 (VGAM485) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22196] VGAM485 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM485 was detected is described hereinabove with reference to Figs. 1–8.

[22197] VGAM485 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus.

VGAM485 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22198] VGAM485 gene encodes a VGAM485 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM485 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM485 precursor RNA is designated SEQ ID:471, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:471 is located at position 1462 relative to the genome of Hepatitis G Virus.

[22199] VGAM485 precursor RNA folds onto itself, forming VGAM485 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22200] An enzyme complex designated DICER COMPLEX, `dices` the VGAM485 folded precursor RNA into VGAM485 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 70%) nucleotide sequence of VGAM485 RNA is designated SEQ ID:3196, and is provided hereinbelow with reference to the sequence listing part.

[22201] VGAM485 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM485 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM485 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22202] VGAM485 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM485 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM485 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM485 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM485 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22203] The complementary binding of VGAM485 RNA, herein designated VGAM RNA, to host target binding sites on



VGAM485 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM485 host target RNA into VGAM485 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22204] It is appreciated that VGAM485 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM485 host target genes. The mRNA of each one of this plurality of VGAM485 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM485 RNA, herein designated VGAM RNA, and which when bound by VGAM485 RNA causes inhibition of translation of respective one or more VGAM485 host target proteins.

[22205] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM485 gene, herein designated VGAM GENE, on one or more VGAM485 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22206] It is yet further appreciated that a function of VGAM485 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM485 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM485 correlate with, and may be deduced from, the identity of the host target genes which VGAM485 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22207] Nucleotide sequences of the VGAM485 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM485 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM485 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM485 are further described hereinbelow with reference to Table 1.

[22208] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM485 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM485 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22209] As mentioned hereinabove with reference to Fig. 1, a function of VGAM485 gene, herein designated VGAM is inhibition of expression of VGAM485 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM485 correlate with, and may be deduced from, the identity of the target genes which VGAM485 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22210] LOC200014 (Accession XM\_114087) is a VGAM485 host target gene. LOC200014 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200014, corresponding to a HOST TAR-

GET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200014 BINDING SITE, designated SEQ ID:42695, to the nucleotide sequence of VGAM485 RNA, herein designated VGAM RNA, also designated SEQ ID:3196.

[22211] A function of VGAM485 is therefore inhibition of LOC200014 (Accession XM\_114087). Accordingly, utilities of VGAM485 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200014. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 486 (VGAM486) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22212] VGAM486 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM486 was detected is described hereinabove with reference to Figs. 1–8.

[22213] VGAM486 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus.

VGAM486 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22214] VGAM486 gene encodes a VGAM486 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM486 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM486 precursor RNA is designated SEQ ID:472, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:472 is located at position 5080 relative to the genome of Hepatitis G Virus.

[22215] VGAM486 precursor RNA folds onto itself, forming VGAM486 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22216] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM486 folded precursor RNA into VGAM486 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM486 RNA is designated SEQ ID:3197, and is provided hereinbelow with reference to the sequence listing part.

[22217] VGAM486 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM486 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM486 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22218] VGAM486 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM486 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM486 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM486 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM486 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22219] The complementary binding of VGAM486 RNA, herein designated VGAM RNA, to host target binding sites on VGAM486 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM486 host target RNA into VGAM486 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22220] It is appreciated that VGAM486 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM486 host target genes. The mRNA of each one of this plurality of VGAM486 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM486 RNA, herein designated VGAM RNA, and which when bound by VGAM486 RNA causes inhibition of translation of respective one or more VGAM486 host target proteins.

[22221] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM486 gene, herein designated VGAM GENE, on one or more VGAM486 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are



also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22222] It is yet further appreciated that a function of VGAM486 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM486 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM486 correlate with, and may be deduced from, the identity of the host target genes which VGAM486 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22223] Nucleotide sequences of the VGAM486 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM486 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM486 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM486 are further described hereinbelow with reference to Table 1.

[22224] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM486 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM486 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22225] As mentioned hereinabove with reference to Fig. 1, a function of VGAM486 gene, herein designated VGAM is inhibition of expression of VGAM486 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM486 correlate with, and may be deduced from, the identity of the target genes which VGAM486 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22226] Beta-site APP-cleaving Enzyme 2 (BACE2, Accession NM\_138992) is a VGAM486 host target gene. BACE2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BACE2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACE2 BINDING SITE, designated SEQ ID:29092, to the

nucleotide sequence of VGAM486 RNA, herein designated VGAM RNA, also designated SEQ ID:3197.

[22227] A function of VGAM486 is therefore inhibition of Beta-site APP-cleaving Enzyme 2 (BACE2, Accession NM\_138992), a gene which cleaves intracellularly the b-secretase site of amyloid precursor protein. Accordingly, utilities of VGAM486 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACE2. The function of BACE2 has been established by previous studies. Deposition in the brain of the 39- to 43-amino acid amyloid-beta peptide is a hallmark of Alzheimer disease (AD; 104300), a frequent complication of Down syndrome (OMIM Ref. No. 190685) patients after age 30 years. Amyloid-beta is generated by proteolytic processing of the amyloid precursor protein (APP; 104760) by beta- and gamma-secretase at the N and C termini, respectively. Presenilin-1 (OMIM Ref. No. 104311) is involved in the gamma-secretase activity. BACE (OMIM Ref. No. 604252), a transmembrane aspartyl protease, possesses beta-secretase activity. By differential display RT-PCR of poorly and highly metastatic breast cancer cell lines, followed by screening a bone marrow stroma cell cDNA library, Xin et al. (2000) obtained a cDNA encoding

BACE2, which they termed ALP56. Sequence analysis predicted that the 518-amino acid protein has 2 pepsin-like active centers, a signal sequence, a propeptide, and a long C-terminal extension including a transmembrane domain. Northern blot analysis detected 2.5- and 2.0-kb transcripts in metastatic tumors injected in SCID mice (see OMIM Ref. No. 202500). In situ hybridization analysis demonstrated high expression in breast, colon, and prostate cancer biopsies, as well as in normal prostate. Northern blot analysis of normal tissue revealed expression in prostate, pancreas, and placenta. Further exposure detected expression in all tissues tested except brain and lymphocytes. Western blot analysis showed expression of a 60-kD protein as well as apparent autocleavage products of 17 and 14 kD. By searching EST databases with the BACE sequence and identifying mapped sequences, Saunders et al. (1999) identified a cDNA encoding BACE2 and mapped the gene to 21q22.2-q22.3. Using FISH, Acquati et al. (2000) confirmed the localization of BACE2 to 21q22.3, within the Down syndrome critical region.

[22228] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [22229] Xin, H.; Stephans, J. C.; Duan, X.; Harrowe, G.; Kim, E.; Grieshammer, U.; Kingsley, C.; Giese, K. : Identification of a novel aspartic-like protease differentially expressed in human breast cancer cell lines. *Biochim. Biophys. Acta* 1501: 125–137, 2000. ; and
- [22230] Saunders, A. J.; Kim, T.-W.; Tanzi, R. E. : BACE maps to chromosome 11 and a BACE homolog, BACE2, reside in the obligate Down syndrome region of chromosome 21. *Science* 286: 1255A only.
- [22231] Further studies establishing the function and utilities of BACE2 are found in John Hopkins OMIM database record ID 605668, and in cited publications numbered 641 and 6416–6419 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC254314 (Accession XM\_172871) is another VGAM486 host target gene. LOC254314 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC254314, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254314 BINDING SITE, designated SEQ ID:46150, to the nucleotide sequence of VGAM486 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3197.

[22232] Another function of VGAM486 is therefore inhibition of LOC254314 (Accession XM\_172871). Accordingly, utilities of VGAM486 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254314. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 487 (VGAM487) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22233] VGAM487 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM487 was detected is described hereinabove with reference to Figs. 1–8.

[22234] VGAM487 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM487 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22235] VGAM487 gene encodes a VGAM487 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM487 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM487 precursor RNA is designated SEQ ID:473, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:473 is located at position 9016 relative to the genome of Hepatitis G Virus.

[22236] VGAM487 precursor RNA folds onto itself, forming VGAM487 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22237] An enzyme complex designated DICER COMPLEX, `dices` the VGAM487 folded precursor RNA into VGAM487 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM487 RNA is designated SEQ ID:3198, and is provided hereinbelow with reference to the sequence listing part.

[22238] VGAM487 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM487 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM487 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[22239] VGAM487 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM487 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM487 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and



BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM487 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM487 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22240] The complementary binding of VGAM487 RNA, herein designated VGAM RNA, to host target binding sites on VGAM487 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM487 host target RNA into VGAM487 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22241] It is appreciated that VGAM487 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM487 host target genes. The mRNA of

each one of this plurality of VGAM487 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM487 RNA, herein designated VGAM RNA, and which when bound by VGAM487 RNA causes inhibition of translation of respective one or more VGAM487 host target proteins.

[22242] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM487 gene, herein designated VGAM GENE, on one or more VGAM487 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[22243] It is yet further appreciated that a function of VGAM487 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM487 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM487 correlate with, and may be deduced from, the identity of the host target genes which VGAM487 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22244] Nucleotide sequences of the VGAM487 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM487 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM487 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM487 are further described hereinbelow with reference to Table 1.

[22245] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM487 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM487 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[22246] As mentioned hereinabove with reference to Fig. 1, a function of VGAM487 gene, herein designated VGAM is inhibition of expression of VGAM487 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM487 correlate with, and may be deduced from, the identity of the target genes which VGAM487 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22247] Interferon (alpha, beta and omega) Receptor 2 (IFNAR2, Accession NM\_000874) is a VGAM487 host target gene. IFNAR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IFNAR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IFNAR2 BINDING SITE, designated SEQ ID:6554, to the nucleotide sequence of VGAM487 RNA, herein designated VGAM RNA, also designated SEQ ID:3198.

[22248] A function of VGAM487 is therefore inhibition of Interferon (alpha, beta and omega) Receptor 2 (IFNAR2, Accession NM\_000874), a gene which is a receptor for interfer-

ons alpha and beta. Accordingly, utilities of VGAM487 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IFNAR2. The function of IFNAR2 has been established by previous studies. Alpha-type antiviral protein is a factor, presumably protein in nature, that mediates specific interferon inhibition of virus replication. According to studies of mouse-man hybrid clones, the locus determining this protein is carried on chromosome 21 (Tan et al., 1973). Tan et al. (1974) made observations of dosage effect in monosomy-21 and trisomy-21 cells which supported assignment of the locus to chromosome 21. This character was also called interferon sensitivity (IS). Chany et al. (1975) showed that trisomy-21 cells have increased interferon sensitivity. Trisomy-16 cells have reduced sensitivity. This might suggest the presence on chromosome 16 of a regulator of mouse antiviral protein. Reve et al. (1976) showed that antibody to a cell surface component coded by human chromosome 21 inhibited the action of interferon. This suggested that antiviral protein is an interferon receptor. See 147570, 147640, 147660 for a discussion of the gamma, beta, and alpha interferons, respectively. De Clercq et al. (1976) concluded that it is not a cell mem-

brane receptor for interferon that is encoded by chromosome 21 Raziuddin et al. (1984) showed that the receptors for alpha- and beta-interferons are specified by chromosome 21. It was presumed that separate genes encoded the alpha- and beta-interferon receptors. Novick et al. (1994) described a universal ligand-binding receptor for human interferons alpha and interferon beta. Sarkar and Gupta (1984) showed that gamma-interferon binds to a separate receptor that is carried by WISH cells (a human amnion cell line). The gene for the receptor was designated also IFNAR. Langer et al. (1990) sublocalized the IFNAR gene to 21q22.1-q22.2 by hybridization of (32)P-labeled recombinant interferon-alpha/beta receptor with human-hamster somatic cell hybrids containing various fragments of human chromosome 21. By in situ hybridization, Lutfalla et al. (1990) refined the assignment to 21q22.1. Lutfalla et al. (1992) further refined the localization by pulsed field gel electrophoresis and its linkage to adjacent markers. They compared the exon structure of the IFNAR gene with that of the genes for receptors of the cytokine/growth hormone/prolactin/interferon receptor family and concluded that they have a common origin and have diverged from the immunoglobulin superfamily with

which they share a common ancestor. Cellular responses to cytokines involve cross-communication through their respective receptors. The IFNs alpha, beta, and gamma mediate innate immune responses to viral infection through IFNAR1/IFNAR2 (OMIM Ref. No. 602376) for IFNA and IFNB, and IFNGR1 (OMIM Ref. No. 107470)/IFNGR2 (OMIM Ref. No. 147569) for IFNG. Stimulation of these receptors activates Janus protein kinases (e.g., JAK1, 147795 and JAK2, 147796), which leads to the tyrosine phosphorylation of STAT1 (OMIM Ref. No. 600555) and STAT2 (OMIM Ref. No. 600556). Although the IFN receptors are expressed at low levels in cells, they may be clustered in the cell membrane to permit efficient signal transduction. Using mouse embryonic fibroblasts (MEFs) from IFNAR1- and IFNGR1-deficient mice, Takaoka et al. (2000) observed that the STAT1-mediated DNA-binding activity and the antiviral response to IFNG in IFNAR-null MEFs but not to IFNA in IFNGR-null MEFs are impaired. Restoration of the IFNG response requires constitutive subthreshold IFNA/IFNB signaling and an intact IFNAR1 capable of interacting with STAT1 after tyrosine phosphorylation. Immunoblot analysis showed that IFNAR1 coimmunoprecipitated with the nonligand-binding component,

IFNGR2, of the IFNGR complex in wildtype MEFs but less well in IFNB-null MEFs. Immunoblot analysis also demonstrated that the IFN receptor components are exclusively localized in the caveolar membrane fractions (see OMIM Ref. No. CAV1; 601047) where there is a concentration of cytoplasmically oriented signaling molecules.

[22249] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22250] Takaoka, A.; Mitani, Y.; Suemori, H.; Sato, M.; Yokochi, T.; Noguchi, S.; Tanaka, N.; Taniguchi, T. : Cross talk between interferon-gamma and -alpha/beta signaling components in caveolar membrane domains. Science 288: 2357-2360, 2000. ; and

[22251] Novick, D.; Cohen, B.; Rubinstein, M. : The human interferon alpha/beta receptor: characterization and molecular cloning. Cell 77: 391-400, 1994.

[22252] Further studies establishing the function and utilities of IFNAR2 are found in John Hopkins OMIM database record ID 602376, and in cited publications numbered 5597-5599, 560 and 11830-5601 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ14621 (Accession NM\_032811) is



another VGAM487 host target gene. FLJ14621 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ14621, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14621 BINDING SITE, designated SEQ ID:26578, to the nucleotide sequence of VGAM487 RNA, herein designated VGAM RNA, also designated SEQ ID:3198.

[22253] Another function of VGAM487 is therefore inhibition of FLJ14621 (Accession NM\_032811). Accordingly, utilities of VGAM487 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14621. FLJ22169 (Accession NM\_024085) is another VGAM487 host target gene. FLJ22169 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22169, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22169 BINDING SITE, designated SEQ ID:23521, to the nucleotide sequence of VGAM487 RNA, herein designated VGAM RNA, also designated SEQ ID:3198.

[22254] Another function of VGAM487 is therefore inhibition of FLJ22169 (Accession NM\_024085). Accordingly, utilities of VGAM487 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22169. RBAK (Accession NM\_021163) is another VGAM487 host target gene. RBAK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RBAK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RBAK BINDING SITE, designated SEQ ID:22140, to the nucleotide sequence of VGAM487 RNA, herein designated VGAM RNA, also designated SEQ ID:3198.

[22255] Another function of VGAM487 is therefore inhibition of RBAK (Accession NM\_021163). Accordingly, utilities of VGAM487 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RBAK. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 488 (VGAM488) viral gene, which modulates expression of respective host target genes thereof, the function and

utility of which host target genes is known in the art.

[22256] VGAM488 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM488 was detected is described hereinabove with reference to Figs. 1–8.

[22257] VGAM488 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM488 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22258] VGAM488 gene encodes a VGAM488 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM488 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM488 precursor RNA is designated SEQ ID:474, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:474 is located at position 2231 relative to the genome of Hepatitis G Virus.

[22259] VGAM488 precursor RNA folds onto itself, forming VGAM488 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[22260] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM488 folded precursor RNA into VGAM488 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 45%) nucleotide se-  
quence of VGAM488 RNA is designated SEQ ID:3199, and  
is provided hereinbelow with reference to the sequence  
listing part.

[22261] VGAM488 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM488 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM488 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[22262] VGAM488 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM488 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM488 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM488 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM488 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[22263] The complementary binding of VGAM488 RNA, herein designated VGAM RNA, to host target binding sites on VGAM488 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM488 host target RNA into VGAM488 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22264] It is appreciated that VGAM488 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM488 host target genes. The mRNA of each one of this plurality of VGAM488 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM488 RNA, herein designated VGAM RNA, and which when bound by VGAM488 RNA causes inhibition of translation of respective one or more VGAM488 host target proteins.

[22265] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM488 gene, herein designated VGAM GENE, on one or

more VGAM488 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22266] It is yet further appreciated that a function of VGAM488 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM488 correlate with, and may be deduced from, the identity of the host target genes which VGAM488 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22267] Nucleotide sequences of the VGAM488 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM488 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM488 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM488 are further described hereinbelow with reference to Table 1.

[22268] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM488 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM488 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22269] As mentioned hereinabove with reference to Fig. 1, a function of VGAM488 gene, herein designated VGAM is inhibition of expression of VGAM488 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM488 correlate with, and may be deduced from, the identity of the target genes which VGAM488 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22270] Cyclin-dependent Kinase (CDC2-like) 10 (CDK10, Acces-



sion NM\_052988) is a VGAM488 host target gene. CDK10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDK10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDK10 BINDING SITE, designated SEQ ID:27558, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22271] A function of VGAM488 is therefore inhibition of Cyclin-dependent Kinase (CDC2-like) 10 (CDK10, Accession NM\_052988), a gene which plays a pivotal role in the regulation of the eukaryotic cell cycle. Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDK10. The function of CDK10 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM193. Cytokine Inducible SH2-containing Protein (CISH, Accession NM\_145071) is another VGAM488 host target gene. CISH BINDING SITE1 and CISH BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CISH, corresponding to HOST

TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CISH BINDING SITE1 and CISH BINDING SITE2, designated SEQ ID:29705 and SEQ ID:14972 respectively, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22272] Another function of VGAM488 is therefore inhibition of Cytokine Inducible SH2-containing Protein (CISH, Accession NM\_145071), a gene which intervenes in the negative regulation of cytokines. Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CISH. The function of CISH has been established by previous studies. As part of the search for immediate-early cytokine-responsive genes, Yoshimura et al. (1995) cloned murine Cish, which was shown to have a growth inhibitory function. Cis, the protein product of Cish, has a Src homology 2 (SH2) domain in the middle of its sole structural motif. Tight linkage of Cish to the Gnai2 gene (OMIM Ref. No. 139360) on mouse chromosome 9, a region syntenic to human 3p21, prompted Uchida et al. (1997) to isolate a human CISH cDNA and map the gene to 3p21.3 by fluorescence in situ

hybridization. Northern blot analysis showed expression of CISH as a 2-kb transcript in various epithelial tissues, including lung and kidney, which develop tumors frequently exhibiting 3p21.3 deletions. The CISH gene contains 2 introns, about 3 kb and 0.4 kb in size, and has 3 repeats of the pentameric mRNA destabilization signal, ATTTA, in its 3-prime untranslated region. The CIS protein consists of 258 amino acids.

[22273] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22274] Uchida, K.; Yoshimura, A.; Inazawa, J.; Yanagisawa, K.; Osada, H.; Masuda, A.; Saito, T.; Takahashi, T.; Miyajima, A.; Takahashi, T. : Molecular cloning of CISH, chromosome assignment to 3p21.3, and analysis of expression in fetal and adult tissues. *Cytogenet. Cell Genet.* 78: 209–212, 1997. ; and

[22275] Yoshimura, A.; Ohkubo, T.; Kiguchi, T.; Jenkins, N. A.; Gilbert, D. J.; Copeland, N. G.; Hara, T.; Miyajima, A. : A novel cytokine-inducible gene CIS, encodes an SH2-containing protein.

[22276] Further studies establishing the function and utilities of CISH are found in John Hopkins OMIM database record ID

602441, and in cited publications numbered 5610–5611 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. MHC Class II Transactivator (MHC2TA, Accession NM\_000246) is another VGAM488 host target gene. MHC2TA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MHC2TA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MHC2TA BINDING SITE, designated SEQ ID:5780, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22277] Another function of VGAM488 is therefore inhibition of MHC Class II Transactivator (MHC2TA, Accession NM\_000246). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MHC2TA. POU Domain, Class 2, Associating Factor 1 (POU2AF1, Accession NM\_006235) is another VGAM488 host target gene. POU2AF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POU2AF1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POU2AF1 BINDING SITE, designated SEQ ID:12891, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22278] Another function of VGAM488 is therefore inhibition of POU Domain, Class 2, Associating Factor 1 (POU2AF1, Accession NM\_006235), a gene which is a transcriptional coactivator that specifically associates with either oct1 or oct2. Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POU2AF1. The function of POU2AF1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM171.Stearoyl-CoA Desaturase (delta-9-desaturase) (SCD, Accession NM\_005063) is another VGAM488 host target gene. SCD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of SCD BINDING SITE, designated SEQ ID:11497, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22279] Another function of VGAM488 is therefore inhibition of Stearoyl-CoA Desaturase (delta-9-desaturase) (SCD, Accession NM\_005063), a gene which functions in the synthesis of unsaturated fatty acids. Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCD. The function of SCD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM314.Solute Carrier Family 6 (neurotransmitter transporter, creatine), Member 8 (SLC6A8, Accession NM\_005629) is another VGAM488 host target gene. SLC6A8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC6A8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC6A8 BINDING SITE, designated SEQ ID:12151, to the nucleotide sequence of VGAM488 RNA,

herein designated VGAM RNA, also designated SEQ ID:3199.

[22280] Another function of VGAM488 is therefore inhibition of Solute Carrier Family 6 (neurotransmitter transporter, creatine), Member 8 (SLC6A8, Accession NM\_005629). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC6A8. Suppressor of Fused Homolog (Drosophila) (SUFU, Accession NM\_016169) is another VGAM488 host target gene. SUFU BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SUFU, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SUFU BINDING SITE, designated SEQ ID:18253, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22281] Another function of VGAM488 is therefore inhibition of Suppressor of Fused Homolog (Drosophila) (SUFU, Accession NM\_016169). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SUFU. Dynactin 4 (p62)

(DCTN4, Accession XM\_041993) is another VGAM488 host target gene. DCTN4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DCTN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DCTN4 BINDING SITE, designated SEQ ID:33667, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22282] Another function of VGAM488 is therefore inhibition of Dynactin 4 (p62) (DCTN4, Accession XM\_041993). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DCTN4. DKFZP434P0111 (Accession XM\_041116) is another VGAM488 host target gene. DKFZP434P0111 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434P0111, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434P0111 BINDING SITE, designated SEQ ID:33458, to the nucleotide sequence of



VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22283] Another function of VGAM488 is therefore inhibition of DKFZP434P0111 (Accession XM\_041116). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434P0111. EFA6R (Accession NM\_015310) is another VGAM488 host target gene. EFA6R BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EFA6R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EFA6R BINDING SITE, designated SEQ ID:17625, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22284] Another function of VGAM488 is therefore inhibition of EFA6R (Accession NM\_015310). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EFA6R. HEMK (Accession NM\_016173) is another VGAM488 host target gene. HEMK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by HEMK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HEMK BINDING SITE, designated SEQ ID:18273, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22285] Another function of VGAM488 is therefore inhibition of HEMK (Accession NM\_016173). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HEMK. KIAA1615 (Accession XM\_044021) is another VGAM488 host target gene. KIAA1615 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1615, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1615 BINDING SITE, designated SEQ ID:34085, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22286] Another function of VGAM488 is therefore inhibition of KIAA1615 (Accession XM\_044021). Accordingly, utilities

of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1615. UQCR (Accession NM\_006830) is another VGAM488 host target gene. UQCR BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by UQCR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UQCR BINDING SITE, designated SEQ ID:13711, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22287] Another function of VGAM488 is therefore inhibition of UQCR (Accession NM\_006830). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UQCR. ZF5128 (Accession NM\_014347) is another VGAM488 host target gene. ZF5128 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZF5128, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZF5128 BINDING SITE, designated

SEQ ID:15670, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22288] Another function of VGAM488 is therefore inhibition of ZF5128 (Accession NM\_014347). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZF5128. LOC152273 (Accession XM\_087429) is another VGAM488 host target gene. LOC152273 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152273 BINDING SITE, designated SEQ ID:39247, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22289] Another function of VGAM488 is therefore inhibition of LOC152273 (Accession XM\_087429). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152273. LOC157381 (Accession XM\_098754) is another VGAM488 host target gene. LOC157381 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC157381, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157381 BINDING SITE, designated SEQ ID:41790, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22290] Another function of VGAM488 is therefore inhibition of LOC157381 (Accession XM\_098754). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157381. LOC157753 (Accession XM\_088381) is another VGAM488 host target gene. LOC157753 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC157753, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157753 BINDING SITE, designated SEQ ID:39661, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22291] Another function of VGAM488 is therefore inhibition of

LOC157753 (Accession XM\_088381). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157753. LOC221250 (Accession XM\_166301) is another VGAM488 host target gene. LOC221250 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221250, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221250 BINDING SITE, designated SEQ ID:44121, to the nucleotide sequence of VGAM488 RNA, herein designated VGAM RNA, also designated SEQ ID:3199.

[22292] Another function of VGAM488 is therefore inhibition of LOC221250 (Accession XM\_166301). Accordingly, utilities of VGAM488 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221250. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 489 (VGAM489) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[22293] VGAM489 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM489 was detected is described hereinabove with reference to Figs. 1–8.

[22294] VGAM489 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM489 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22295] VGAM489 gene encodes a VGAM489 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM489 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM489 precursor RNA is designated SEQ ID:475, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:475 is located at position 8122 relative to the genome of Hepatitis G Virus.

[22296] VGAM489 precursor RNA folds onto itself, forming VGAM489 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[22297] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM489 folded precursor RNA into VGAM489 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 45%) nucleotide se-  
quence of VGAM489 RNA is designated SEQ ID:3200, and  
is provided hereinbelow with reference to the sequence  
listing part.

[22298] VGAM489 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM489 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM489 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region



and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[22299] VGAM489 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM489 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM489 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM489 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM489 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[22300] The complementary binding of VGAM489 RNA, herein designated VGAM RNA, to host target binding sites on VGAM489 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM489 host target RNA into VGAM489 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22301] It is appreciated that VGAM489 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM489 host target genes. The mRNA of each one of this plurality of VGAM489 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM489 RNA, herein designated VGAM RNA, and which when bound by VGAM489 RNA causes inhibition of translation of respective one or more VGAM489 host target proteins.

[22302] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM489 gene, herein designated VGAM GENE, on one or

more VGAM489 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22303] It is yet further appreciated that a function of VGAM489 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM489 correlate with, and may be deduced from, the identity of the host target genes which VGAM489 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22304] Nucleotide sequences of the VGAM489 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM489 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM489 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM489 are further described hereinbelow with reference to Table 1.

[22305] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM489 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM489 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22306] As mentioned hereinabove with reference to Fig. 1, a function of VGAM489 gene, herein designated VGAM is inhibition of expression of VGAM489 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM489 correlate with, and may be deduced from, the identity of the target genes which VGAM489 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22307] Active BCR-related Gene (ABR, Accession NM\_001092) is a

VGAM489 host target gene. ABR BINDING SITE1 and ABR BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABR, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABR BINDING SITE1 and ABR BINDING SITE2, designated SEQ ID:6747 and SEQ ID:22492 respectively, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22308] A function of VGAM489 is therefore inhibition of Active BCR-related Gene (ABR, Accession NM\_001092), a gene which gtpase-activating protein for rac and cdc42. Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABR. The function of ABR has been established by previous studies. Heisterkamp et al. (1989) described an active BCR-related gene (ABR) that they identified based on its homology with the BCR gene (OMIM Ref. No. 151410) located on chromosome 22. BCR is involved in reciprocal translocations with the ABL oncogene (OMIM Ref. No. 189980) on chromosome 9 in Philadelphia chromosome-positive chronic myelogenous leukemia. Heis-

terkamp et al. (1993) mapped the ABR gene to 17p13.3 by in situ hybridization techniques. McDonald et al. (1994) found that the ABR locus was deleted in 7 of 8 informative cases of medulloblastoma. Using pulsed field gel electrophoresis, they localized a polymorphic marker of the ABR gene to within 220 kb of D17S34. A cosmid contig constructed in this region was used to demonstrate by fluorescence in situ hybridization that the 5-prime to 3-prime transcriptional orientation of the ABR gene is toward the telomere.

[22309] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22310] Heisterkamp, N.; Kaartinen, V.; van Soest, S.; Bokoch, G. M.; Groffen, J. : Human ABR encodes a protein with GAP-rac activity and homology to the DBL nucleotide exchange factor domain. J. Biol. Chem. 268: 16903–16906, 1993. ; and

[22311] McDonald, J. D.; Daneshvar, L.; Willert, J. R.; Matsumura, K.; Waldman, F.; Cogen, P. H. : Physical mapping of chromosome 17p13.3 in the region of a putative tumor suppressor gene import.

[22312] Further studies establishing the function and utilities of

ABR are found in John Hopkins OMIM database record ID 600365, and in cited publications numbered 7740–7742 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fibroblast Growth Factor Receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome) (FGFR2, Accession NM\_000141) is another VGAM489 host target gene. FGFR2 BINDING SITE1 through FGFR2 BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGFR2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGFR2 BINDING SITE1 through FGFR2 BINDING SITE6, designated SEQ ID:5637, SEQ ID:23233, SEQ ID:23240, SEQ ID:23287, SEQ ID:23293 and SEQ ID:23299 respectively, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22313] Another function of VGAM489 is therefore inhibition of Fibroblast Growth Factor Receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial

dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome) (FGFR2, Accession NM\_000141). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGFR2. HTRA3 (Accession XM\_114416) is another VGAM489 host target gene. HTRA3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HTRA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HTRA3 BINDING SITE, designated SEQ ID:42937, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22314] Another function of VGAM489 is therefore inhibition of HTRA3 (Accession XM\_114416). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTRA3. Apolipoprotein L, 2 (APOL2, Accession NM\_030882) is another VGAM489 host target gene. APOL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APOL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-



ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APOL2 BINDING SITE, designated SEQ ID:25158, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22315] Another function of VGAM489 is therefore inhibition of Apolipoprotein L, 2 (APOL2, Accession NM\_030882). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOL2. FLJ10900 (Accession XM\_037744) is another VGAM489 host target gene. FLJ10900 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10900, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10900 BINDING SITE, designated SEQ ID:32668, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22316] Another function of VGAM489 is therefore inhibition of FLJ10900 (Accession XM\_037744). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10900.

FLJ12154 (Accession NM\_021944) is another VGAM489 host target gene. FLJ12154 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ12154, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12154 BINDING SITE, designated SEQ ID:22465, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22317] Another function of VGAM489 is therefore inhibition of FLJ12154 (Accession NM\_021944). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12154. G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_057169) is another VGAM489 host target gene. GIT2 BINDING SITE1 through GIT2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GIT2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GIT2 BINDING SITE1 through GIT2 BINDING SITE3, designated SEQ

ID:27682, SEQ ID:27695 and SEQ ID:16600 respectively, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22318] Another function of VGAM489 is therefore inhibition of G Protein-coupled Receptor Kinase-interactor 2 (GIT2, Accession NM\_057169). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GIT2. KIAA0157 (Accession NM\_032182) is another VGAM489 host target gene. KIAA0157 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0157, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0157 BINDING SITE, designated SEQ ID:25898, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22319] Another function of VGAM489 is therefore inhibition of KIAA0157 (Accession NM\_032182). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0157. KIAA0258 (Accession NM\_014785) is another

VGAM489 host target gene. KIAA0258 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0258, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0258 BINDING SITE, designated SEQ ID:16640, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22320] Another function of VGAM489 is therefore inhibition of KIAA0258 (Accession NM\_014785). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0258. SSB-3 (Accession NM\_080861) is another VGAM489 host target gene. SSB-3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSB-3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSB-3 BINDING SITE, designated SEQ ID:28103, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22321] Another function of VGAM489 is therefore inhibition of SSB-3 (Accession NM\_080861). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSB-3. LOC143173 (Accession XM\_016685) is another VGAM489 host target gene. LOC143173 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC143173, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143173 BINDING SITE, designated SEQ ID:30270, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22322] Another function of VGAM489 is therefore inhibition of LOC143173 (Accession XM\_016685). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143173. LOC144266 (Accession XM\_084795) is another VGAM489 host target gene. LOC144266 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC144266, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144266 BINDING SITE, designated SEQ ID:37710, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22323] Another function of VGAM489 is therefore inhibition of LOC144266 (Accession XM\_084795). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144266. LOC145188 (Accession XM\_085049) is another VGAM489 host target gene. LOC145188 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145188, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145188 BINDING SITE, designated SEQ ID:37809, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22324] Another function of VGAM489 is therefore inhibition of LOC145188 (Accession XM\_085049). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC145188. LOC151701 (Accession XM\_098109) is another VGAM489 host target gene. LOC151701 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151701, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151701 BINDING SITE, designated SEQ ID:41386, to the nucleotide sequence of VGAM489 RNA, herein designated VGAM RNA, also designated SEQ ID:3200.

[22325] Another function of VGAM489 is therefore inhibition of LOC151701 (Accession XM\_098109). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151701. LOC92912 (Accession XM\_047970) is another VGAM489 host target gene. LOC92912 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92912, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92912 BINDING SITE, designated SEQ ID:35084, to the nucleotide sequence of VGAM489 RNA, herein designated

VGAM RNA, also designated SEQ ID:3200.

[22326] Another function of VGAM489 is therefore inhibition of LOC92912 (Accession XM\_047970). Accordingly, utilities of VGAM489 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92912. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 490 (VGAM490) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22327] VGAM490 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM490 was detected is described hereinabove with reference to Figs. 1–8.

[22328] VGAM490 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM490 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22329] VGAM490 gene encodes a VGAM490 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other



miRNA genes, and unlike most ordinary genes, VGAM490 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM490 precursor RNA is designated SEQ ID:476, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:476 is located at position 776 relative to the genome of Hepatitis G Virus.

[22330] VGAM490 precursor RNA folds onto itself, forming VGAM490 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22331] An enzyme complex designated DICER COMPLEX, `dices` the VGAM490 folded precursor RNA into VGAM490 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 83%) nucleotide sequence of VGAM490 RNA is designated SEQ ID:3201, and is provided hereinbelow with reference to the sequence listing part.

[22332] VGAM490 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM490 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM490 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[22333] VGAM490 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM490 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM490 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM490 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM490 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22334] The complementary binding of VGAM490 RNA, herein designated VGAM RNA, to host target binding sites on VGAM490 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM490 host target RNA into VGAM490 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22335] It is appreciated that VGAM490 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM490 host target genes. The mRNA of

each one of this plurality of VGAM490 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM490 RNA, herein designated VGAM RNA, and which when bound by VGAM490 RNA causes inhibition of translation of respective one or more VGAM490 host target proteins.

[22336] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM490 gene, herein designated VGAM GENE, on one or more VGAM490 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[22337] It is yet further appreciated that a function of VGAM490 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM490 correlate with, and may be deduced from, the identity of the host target genes which VGAM490 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[22338] Nucleotide sequences of the VGAM490 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM490 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM490 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM490 are further described hereinbelow with reference to Table 1.

[22339] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM490 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM490 RNA, herein desig–

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[22340] As mentioned hereinabove with reference to Fig. 1, a function of VGAM490 gene, herein designated VGAM is inhibition of expression of VGAM490 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM490 correlate with, and may be deduced from, the identity of the target genes which VGAM490 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22341] Adenylate Cyclase 2 (brain) (ADCY2, Accession XM\_036383) is a VGAM490 host target gene. ADCY2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADCY2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADCY2 BINDING SITE, designated SEQ ID:32432, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22342] A function of VGAM490 is therefore inhibition of Adenylate Cyclase 2 (brain) (ADCY2, Accession XM\_036383), a gene which Adenylate cyclase (type 2), an ATP-

pyrophosphate lyase; converts ATP to cAMP. Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADCY2. The function of ADCY2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM120. Myosin IIIA (MYO3A, Accession XM\_011851) is another VGAM490 host target gene. MYO3A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MYO3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYO3A BINDING SITE, designated SEQ ID:30196, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22343] Another function of VGAM490 is therefore inhibition of Myosin IIIA (MYO3A, Accession XM\_011851), a gene which may have a role in photoreceptor function and/or maintenance. Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYO3A. The function of MYO3A

has been established by previous studies. Actin-dependent motor proteins are members of the large myosin superfamily and are categorized into conventional myosins (class II) and unconventional myosins (classes I and III through XV) based on their variable C-terminal cargo-binding domains. Class III myosins, such as MYO3A, have a kinase domain N-terminal to the conserved N-terminal motor domains and are expressed in photoreceptors. Walsh et al. (2002) showed that normal hearing in humans requires myosin IIIA, which is the human homolog of NINAC, a class III myosin that is required for normal vision in *Drosophila*. In an extended Israeli family, they showed that nonsyndromic progressive hearing loss is caused by 3 different recessive, loss of function mutations in myosin IIIA. Of 18 affected relatives in this family, 7 were homozygous and 11 were compound heterozygous for pairs of mutant alleles. Expression of mammalian myosin IIIA is highly restricted, with the strongest expression in retina and cochlea. The involvement of homologous class III myosins in both *Drosophila* vision and human hearing is an evolutionary link between these sensory systems.

[22344] Full details of the abovementioned studies are described



in the following publications, the disclosure of which are hereby incorporated by reference:

[22345] Dose, A. C.; Burnside, B. : Cloning and chromosomal localization of a human class III myosin. Genomics 67: 333–342, 2000. ; and

[22346] Walsh, T.; Walsh, V.; Vreugde, S.; Hertzano, R.; Shahin, H.; Haika, S.; Lee, M. K.; Kanaan, M.; King, M.–C.; Avraham, K. B. : From flies' eyes to our ears: mutations in a human class I.

[22347] Further studies establishing the function and utilities of MYO3A are found in John Hopkins OMIM database record ID 606808, and in cited publications numbered 6140–6141 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phospholipase A2, Group IID (PLA2G2D, Accession NM\_012400) is another VGAM490 host target gene. PLA2G2D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLA2G2D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLA2G2D BINDING SITE, designated SEQ ID:14766, to the nucleotide sequence of VGAM490 RNA,

herein designated VGAM RNA, also designated SEQ ID:3201.

[22348] Another function of VGAM490 is therefore inhibition of Phospholipase A2, Group IID (PLA2G2D, Accession NM\_012400), a gene which is involved in phospholipid digestion, remodeling of cell membranes, and host defense, as well as pathophysiologic processes. Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLA2G2D. The function of PLA2G2D and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74.DKFZP564O0423 (Accession XM\_166254) is another VGAM490 host target gene. DKFZP564O0423 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564O0423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564O0423 BINDING SITE, designated SEQ ID:44062, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22349] Another function of VGAM490 is therefore inhibition of DKFZP564O0423 (Accession XM\_166254). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564O0423. FLJ14564 (Accession XM\_084459) is another VGAM490 host target gene. FLJ14564 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14564, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14564 BINDING SITE, designated SEQ ID:37594, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22350] Another function of VGAM490 is therefore inhibition of FLJ14564 (Accession XM\_084459). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14564. KIAA0514 (Accession NM\_014696) is another VGAM490 host target gene. KIAA0514 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0514, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0514 BINDING SITE, designated SEQ ID:16201, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22351] Another function of VGAM490 is therefore inhibition of KIAA0514 (Accession NM\_014696). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0514. KIAA1522 (Accession XM\_036299) is another VGAM490 host target gene. KIAA1522 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1522, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1522 BINDING SITE, designated SEQ ID:32417, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22352] Another function of VGAM490 is therefore inhibition of KIAA1522 (Accession XM\_036299). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1522. KIAA1535 (Accession XM\_086565) is another VGAM490 host target gene. KIAA1535 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1535, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1535 BINDING SITE, designated SEQ ID:38766, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22353] Another function of VGAM490 is therefore inhibition of KIAA1535 (Accession XM\_086565). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1535. KIAA1656 (Accession XM\_038022) is another VGAM490 host target gene. KIAA1656 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1656, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1656 BINDING SITE, designated SEQ ID:32725, to the nucleotide sequence of VGAM490 RNA, herein designated

VGAM RNA, also designated SEQ ID:3201.

[22354] Another function of VGAM490 is therefore inhibition of KIAA1656 (Accession XM\_038022). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1656. MAD4 (Accession NM\_006454) is another VGAM490 host target gene. MAD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAD4 BINDING SITE, designated SEQ ID:13169, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22355] Another function of VGAM490 is therefore inhibition of MAD4 (Accession NM\_006454). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAD4. NKX2B (Accession NM\_002509) is another VGAM490 host target gene. NKX2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NKX2B, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NKX2B BINDING SITE, designated SEQ ID:8342, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22356] Another function of VGAM490 is therefore inhibition of NKX2B (Accession NM\_002509). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NKX2B. Target of Myb1 (chicken) (TOM1, Accession NM\_005488) is another VGAM490 host target gene. TOM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TOM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOM1 BINDING SITE, designated SEQ ID:11984, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22357] Another function of VGAM490 is therefore inhibition of Target of Myb1 (chicken) (TOM1, Accession NM\_005488). Accordingly, utilities of VGAM490 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with TOM1. TP53TG3 (Accession NM\_015369) is another VGAM490 host target gene. TP53TG3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TP53TG3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TP53TG3 BINDING SITE, designated SEQ ID:17668, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22358] Another function of VGAM490 is therefore inhibition of TP53TG3 (Accession NM\_015369). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TP53TG3. LOC149267 (Accession NM\_138480) is another VGAM490 host target gene. LOC149267 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC149267, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149267 BINDING SITE, designated SEQ ID:28830, to the nucleotide se-



quence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22359] Another function of VGAM490 is therefore inhibition of LOC149267 (Accession NM\_138480). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149267. LOC150960 (Accession XM\_087059) is another VGAM490 host target gene. LOC150960 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150960, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150960 BINDING SITE, designated SEQ ID:39030, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22360] Another function of VGAM490 is therefore inhibition of LOC150960 (Accession XM\_087059). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150960. LOC164714 (Accession XM\_104657) is another VGAM490 host target gene. LOC164714 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC164714, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164714 BINDING SITE, designated SEQ ID:42175, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22361] Another function of VGAM490 is therefore inhibition of LOC164714 (Accession XM\_104657). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC164714. LOC203292 (Accession XM\_117527) is another VGAM490 host target gene. LOC203292 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203292, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203292 BINDING SITE, designated SEQ ID:43499, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22362] Another function of VGAM490 is therefore inhibition of LOC203292 (Accession XM\_117527). Accordingly, utilities

of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203292. LOC257364 (Accession XM\_170768) is another VGAM490 host target gene. LOC257364 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257364, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257364 BINDING SITE, designated SEQ ID:45524, to the nucleotide sequence of VGAM490 RNA, herein designated VGAM RNA, also designated SEQ ID:3201.

[22363] Another function of VGAM490 is therefore inhibition of LOC257364 (Accession XM\_170768). Accordingly, utilities of VGAM490 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257364. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 491 (VGAM491) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22364] VGAM491 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM491 was detected is described hereinabove with reference to Figs. 1–8.

[22365] VGAM491 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM491 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22366] VGAM491 gene encodes a VGAM491 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM491 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM491 precursor RNA is designated SEQ ID:477, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:477 is located at position 1627 relative to the genome of Hepatitis G Virus.

[22367] VGAM491 precursor RNA folds onto itself, forming VGAM491 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22368] An enzyme complex designated DICER COMPLEX, `dices` the VGAM491 folded precursor RNA into VGAM491 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM491 RNA is designated SEQ ID:3202, and is provided hereinbelow with reference to the sequence listing part.

[22369] VGAM491 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM491 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM491 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[22370] VGAM491 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM491 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM491 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM491 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM491 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22371] The complementary binding of VGAM491 RNA, herein designated VGAM RNA, to host target binding sites on VGAM491 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM491 host target RNA into VGAM491 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22372] It is appreciated that VGAM491 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM491 host target genes. The mRNA of each one of this plurality of VGAM491 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM491 RNA, herein designated VGAM RNA, and which when bound by VGAM491 RNA causes inhibition of translation of respective one or more VGAM491 host target proteins.

[22373] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM491 gene, herein designated VGAM GENE, on one or more VGAM491 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22374] It is yet further appreciated that a function of VGAM491 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM491 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM491 correlate with, and may be deduced from, the identity of the host target genes which VGAM491 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22375] Nucleotide sequences of the VGAM491 precursor RNA,



herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM491 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM491 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM491 are further  
described hereinbelow with reference to Table 1.

[22376] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM491 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM491 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[22377] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM491 gene, herein designated VGAM is  
inhibition of expression of VGAM491 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM491 correlate with, and may be deduced  
from, the identity of the target genes which VGAM491  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[22378] Casein Kinase 1, Gamma 2 (CSNK1G2, Accession  
NM\_001319) is a VGAM491 host target gene. CSNK1G2

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSNK1G2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSNK1G2 BINDING SITE, designated SEQ ID:7007, to the nucleotide sequence of VGAM491 RNA, herein designated VGAM RNA, also designated SEQ ID:3202.

[22379] A function of VGAM491 is therefore inhibition of Casein Kinase 1, Gamma 2 (CSNK1G2, Accession NM\_001319). Accordingly, utilities of VGAM491 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSNK1G2. KIAA0669 (Accession NM\_014779) is another VGAM491 host target gene. KIAA0669 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0669, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0669 BINDING SITE, designated SEQ ID:16624, to the nucleotide sequence of VGAM491 RNA, herein designated VGAM RNA, also designated SEQ

ID:3202.

[22380] Another function of VGAM491 is therefore inhibition of KIAA0669 (Accession NM\_014779). Accordingly, utilities of VGAM491 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0669. Zinc Finger Protein 36, C3H Type-like 2 (ZFP36L2, Accession NM\_006887) is another VGAM491 host target gene. ZFP36L2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZFP36L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFP36L2 BINDING SITE, designated SEQ ID:13751, to the nucleotide sequence of VGAM491 RNA, herein designated VGAM RNA, also designated SEQ ID:3202.

[22381] Another function of VGAM491 is therefore inhibition of Zinc Finger Protein 36, C3H Type-like 2 (ZFP36L2, Accession NM\_006887). Accordingly, utilities of VGAM491 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFP36L2. LOC147929 (Accession XM\_085961) is another VGAM491 host target gene. LOC147929 BINDING SITE is HOST TARGET binding

site found in the 5' untranslated region of mRNA encoded by LOC147929, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147929 BINDING SITE, designated SEQ ID:38421, to the nucleotide sequence of VGAM491 RNA, herein designated VGAM RNA, also designated SEQ ID:3202.

[22382] Another function of VGAM491 is therefore inhibition of LOC147929 (Accession XM\_085961). Accordingly, utilities of VGAM491 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147929. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 492 (VGAM492) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22383] VGAM492 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM492 was detected is described hereinabove with reference to Figs. 1-8.

[22384] VGAM492 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus.

VGAM492 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22385] VGAM492 gene encodes a VGAM492 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM492 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM492 precursor RNA is designated SEQ ID:478, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:478 is located at position 4128 relative to the genome of Hepatitis G Virus.

[22386] VGAM492 precursor RNA folds onto itself, forming VGAM492 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[22387] An enzyme complex designated DICER COMPLEX, `dices` the VGAM492 folded precursor RNA into VGAM492 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM492 RNA is designated SEQ ID:3203, and is provided hereinbelow with reference to the sequence listing part.

[22388] VGAM492 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM492 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM492 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22389] VGAM492 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM492 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM492 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM492 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM492 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22390] The complementary binding of VGAM492 RNA, herein designated VGAM RNA, to host target binding sites on VGAM492 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM492 host target RNA into VGAM492 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22391] It is appreciated that VGAM492 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM492 host target genes. The mRNA of each one of this plurality of VGAM492 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM492 RNA, herein designated VGAM RNA, and which when bound by VGAM492 RNA causes inhibition of translation of respective one or more VGAM492 host target proteins.

[22392] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM492 gene, herein designated VGAM GENE, on one or more VGAM492 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated



only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22393] It is yet further appreciated that a function of VGAM492 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM492 correlate with, and may be deduced from, the identity of the host target genes which VGAM492 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22394] Nucleotide sequences of the VGAM492 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM492 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM492 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM492 are further described hereinbelow with reference to Table 1.

[22395] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM492 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM492 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22396] As mentioned hereinabove with reference to Fig. 1, a function of VGAM492 gene, herein designated VGAM is inhibition of expression of VGAM492 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM492 correlate with, and may be deduced from, the identity of the target genes which VGAM492 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22397] APG5 Autophagy 5-like (*S. cerevisiae*) (APG5L, Accession NM\_004849) is a VGAM492 host target gene. APG5L BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by APG5L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of APG5L BINDING SITE, designated SEQ ID:11264, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22398] A function of VGAM492 is therefore inhibition of APG5 Autophagy 5-like (*S. cerevisiae*) (APG5L, Accession NM\_004849), a gene which conjugates to apg12 and associates with isolation membrane to form cup-shaped isolation membrane and autophagosome. Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APG5L. The function of APG5L has been established by previous studies. Apoptosis is an active form of cell death and is of fundamental importance in tissue development and homeostasis. Grand et al. (1995) observed that human and rodent cells undergoing apoptosis expressed high levels of a novel 45-kD protein, which they termed apoptosis-specific protein (ASP). They also found ASP in Burkitt lymphoma (OMIM Ref. No. 113970) cells and in adenovirus-transformed human and rat embryo cells induced into apoptosis by a variety of stimuli. The authors did not detect ASP in viable cells or in cells dying passively by necrosis. Microscopy showed high levels of

ASP in the cytoplasm of cells displaying the chromatin condensation and fragmentation patterns typical of apoptosis. The authors observed retention of ASP even when DNA was no longer detectable. Immunofluorescence staining indicated that ASP primarily colocalizes with, but is clearly distinct from, nonmuscle actin (e.g., 102560). Grand et al. (1995) concluded that ASP forms part of, or at least strongly associates with, a modified cytoskeleton unique to cells undergoing apoptosis. Hammond et al. (1998) found that ASP mRNA is present at similar levels in viable and apoptotic cells, whereas ASP protein levels are dramatically higher in apoptotic cells. They concluded that this increase in protein expression is due to increased translation of preexisting ASP mRNA. ASP protein expression is a relatively late event in the apoptotic process, occurring downstream of caspase activity.

[22399] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22400] Grand, R. J. A.; Milner, A. E.; Mustoe, T.; Johnson, G. D.; Owen, D.; Grant, M. L.; Gregory, C. D. : A novel protein expressed in mammalian cells undergoing apoptosis. *Exp. Cell Res.* 218: 439–451, 1995. ; and

[22401] Hammond, E. M.; Brunet, C. L.; Johnson, G. D.; Parkhill, J.; Milner, A. E.; Brady, G.; Gregory, C. D.; Grand, R. J. A. : Homology between a human apoptosis specific protein and the prod.

[22402] Further studies establishing the function and utilities of APG5L are found in John Hopkins OMIM database record ID 604261, and in cited publications numbered 742 and 7435–7436 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Caspase Recruitment Domain Family, Member 4 (CARD4, Accession NM\_006092) is another VGAM492 host target gene. CARD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CARD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CARD4 BINDING SITE, designated SEQ ID:12740, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22403] Another function of VGAM492 is therefore inhibition of Caspase Recruitment Domain Family, Member 4 (CARD4, Accession NM\_006092), a gene which Activates CASP9 to

induce apoptosis, regulates activation of NF- $\kappa$ B. Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CARD4. The function of CARD4 has been established by previous studies. By searching a proprietary EST database for sequences encoding CARD motifs, followed by screening an endothelial cell cDNA library, Bertin et al. (1999) obtained a cDNA encoding CARD4. The deduced 953-amino acid CARD4 protein contains an N-terminal CARD motif, an NBD, and unlike APAF1, 10 tandem leucine-rich repeats in its C terminus. Northern blot analysis revealed abundant expression of a 4.5-kb transcript in adult heart, spleen, and lung, as well as in numerous cancer cell lines and fetal tissues. Yeast 2-hybrid analysis using the CARD domain of CARD4 as bait to screen breast, prostate, and brain cDNA libraries, as well as coimmunoprecipitation analysis, indicated preferential interaction with the CARD of RICK (RIPK2; 603455). Luciferase reporter analysis showed that the CARD domain of CARD4, but not that of APAF1, potently induces activation of nuclear factor  $\kappa$ -B (see OMIM Ref. No. 164011), but not of JUN N-terminal kinase (see OMIM Ref. No. 601158), in a concentration-dependent manner. Us-

ing similar methods, Inohara et al. (1999) cloned and characterized CARD4, which they called NOD1. Northern blot analysis detected wide expression of NOD1. In situ hybridization analysis showed relatively restricted expression of Nod1 in day-15.5 mouse embryos. Confocal microscopy demonstrated that NOD1 is a cytosolic protein. Coimmunoprecipitation analysis revealed that NOD1 preferentially interacts with procaspases containing CARDs or death effector domains (DEDs), as well as with itself, RICK, and CLARP (CFLAR; 603599), but not with RAIDD (CRADD; 603454), APAF1, NIK (OMIM Ref. No. 604655), or other CARD- or DED-containing proteins. Functional analysis indicated that the CARD and NBD of NOD1, but not the LRR, enhance apoptosis induced by CASP9, but not by other caspases or CLARP. The CARD was found to be essential for NOD1 to bind and activate CASP9, as well as to promote apoptosis. Inohara et al. (1999) also observed that NOD1 interacts with RICK in NFkB activation.

[22404] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22405] Bertin, J.; Nir, W.-J.; Fischer, C. M.; Tayber, O. V.; Errada, P. R.; Grant, J. R.; Keilty, J. J.; Gosselin, M. L.; Robison, K. E.;

Wong, G. H. W.; Glucksmann, M. A.; DiStefano, P. S. : Human CARD4 protein is a novel CED-4/Apaf-1 cell death family member that activates NF-kappa-B. J. Biol. Chem. 274: 12955-12958, 1999. ; and

[22406] Inohara, N.; Koseki, T.; del Peso, L.; Hu, Y.; Yee, C.; Chen, S.; Carrio, R.; Merino, J.; Liu, D.; Ni, J.; Nunez, G. : Nod1, an Apaf-1-like activator of caspase-9 and nuclear factor-ka.

[22407] Further studies establishing the function and utilities of CARD4 are found in John Hopkins OMIM database record ID 605980, and in cited publications numbered 6825 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cytoplasmic Linker 2 (CYLN2, Accession NM\_003388) is another VGAM492 host target gene. CYLN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYLN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYLN2 BINDING SITE, designated SEQ ID:9424, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.



[22408] Another function of VGAM492 is therefore inhibition of Cytoplasmic Linker 2 (CYLN2, Accession NM\_003388), a gene which associates with microtubules and dendritic lamellar bodies. Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYLN2. The function of CYLN2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM94. Deoxyribonuclease I (DNASE1, Accession NM\_005223) is another VGAM492 host target gene. DNASE1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DNASE1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNASE1 BINDING SITE, designated SEQ ID:11716, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22409] Another function of VGAM492 is therefore inhibition of Deoxyribonuclease I (DNASE1, Accession NM\_005223), a gene which seems to be involved in cell death. Accord-

ingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNASE1. The function of DNASE1 has been established by previous studies. Systemic lupus erythematosus (SLE; 152700) is a multifactorial autoimmune disease that is said to affect more than 1 million people in the United States. SLE is characterized by the presence of antinuclear antibodies (ANA) directed against naked DNA and entire nucleosomes. It was thought that the resulting immune complexes accumulate in vessel walls, glomeruli, and joints and cause a hypersensitivity reaction type III that manifests as glomerulonephritis, arthritis, and generalized vasculitis. Several studies had suggested that increased liberation or disturbed clearance of nuclear DNA-protein complexes after cell death may initiate and propagate the disease. Consequently, DNASE1, which is a major nuclease present in serum, urine, and secretata, may be responsible for the removal of DNA from nuclear antigens at sites of high cell turnover and thus prevent SLE. To test this hypothesis, Napirei et al. (2000) generated Dnase1-deficient mice by gene targeting. They found that these animals show the classic symptoms of SLE, namely the presence of ANA, the deposition of immune com-

plexes in glomeruli, and full-blown glomerulonephritis in a Dnase1 dose-dependent manner. Moreover, in agreement with earlier reports, they found Dnase1 activities in serum to be lower in SLE patients than in normal subjects. The findings suggested that lack or reduction of Dnase1 is a critical factor in the initiation of human SLE. In 2 females with systemic lupus erythematosus (OMIM Ref. No. 152700), Yasutomo et al. (2001) identified an A-to-G transition in exon 2 at position 172 of the DNASE1 coding sequence, which resulted in a lys-to-ter substitution at codon 5. These female patients, who were 13 and 17 years of age, respectively, were diagnosed as having SLE based on clinical features, high serum titers of antibodies against double-stranded DNA, and Sjogren syndrome. The 2 patients were unrelated and the family members did not have any signs or symptoms of SLE. The patients had substantially lower levels of DNASE1 activity in the sera than in other SLE patients without a DNASE1 mutation. However, the DNASE1 activity of SLE patients without DNASE1 mutations is lower than that of healthy controls. The patient's B cells had 30 to 50% of the DNASE1 activity of cells from controls, showing that heterozygous mutation of DNASE1 reduces the total activity of this enzyme.

[22410] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22411] Napirei, M.; Karsunky, H.; Zevnik, B.; Stephan, H.; Mannherz, H. G.; Moroy, T. : Features of systemic lupus erythematosus in Dnase1-deficient mice. Nature Genet. 25: 177-181, 2000. ; and

[22412] Yasutomo, K.; Horiuchi, T.; Kagami, S.; Tsukamoto, H.; Hashimura, C.; Urushihara, M.; Kuroda, Y. : Mutation of DNASE1 in people with systemic lupus erythematosus. Nature Genet. 28: 31.

[22413] Further studies establishing the function and utilities of DNASE1 are found in John Hopkins OMIM database record ID 125505, and in cited publications numbered 3737-3743 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Potassium Intermediate/small Conductance Calcium-activated Channel, Subfamily N, Member 4 (KCNN4, Accession NM\_002250) is another VGAM492 host target gene. KCNN4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KCNN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of KCNN4 BINDING SITE, designated SEQ ID:8039, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22414] Another function of VGAM492 is therefore inhibition of Potassium Intermediate/small Conductance Calcium-activated Channel, Subfamily N, Member 4 (KCNN4, Accession NM\_002250), a gene which forms a voltage-independent potassium channel that is activated by intracellular calcium. Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNN4. The function of KCNN4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152.ARL8 (Accession XM\_167671) is another VGAM492 host target gene. ARL8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ARL8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARL8 BINDING SITE,

designated SEQ ID:44764, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22415] Another function of VGAM492 is therefore inhibition of ARL8 (Accession XM\_167671). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARL8. Chromosome 17 Open Reading Frame 31 (C17orf31, Accession NM\_017575) is another VGAM492 host target gene. C17orf31 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C17orf31, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C17orf31 BINDING SITE, designated SEQ ID:19007, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22416] Another function of VGAM492 is therefore inhibition of Chromosome 17 Open Reading Frame 31 (C17orf31, Accession NM\_017575). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C17orf31. Diacyl-

glycerol Kinase, Delta 130kDa (DGKD, Accession XM\_002384) is another VGAM492 host target gene. DGKD BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DGKD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGKD BINDING SITE, designated SEQ ID:29887, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22417] Another function of VGAM492 is therefore inhibition of Diacylglycerol Kinase, Delta 130kDa (DGKD, Accession XM\_002384). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DGKD. KIAA1649 (Accession NM\_032311) is another VGAM492 host target gene. KIAA1649 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1649, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1649 BINDING SITE, designated SEQ ID:26110, to the nucleotide sequence of VGAM492

RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22418] Another function of VGAM492 is therefore inhibition of KIAA1649 (Accession NM\_032311). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1649. MBC3205 (Accession NM\_033408) is another VGAM492 host target gene. MBC3205 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MBC3205, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MBC3205 BINDING SITE, designated SEQ ID:27225, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22419] Another function of VGAM492 is therefore inhibition of MBC3205 (Accession NM\_033408). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBC3205. Transducer of ERBB2, 2 (TOB2, Accession XM\_170995) is another VGAM492 host target gene. TOB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by TOB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOB2 BINDING SITE, designated SEQ ID:45769, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22420] Another function of VGAM492 is therefore inhibition of Transducer of ERBB2, 2 (TOB2, Accession XM\_170995). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOB2. Target of Myb1 (chicken) (TOM1, Accession NM\_005488) is another VGAM492 host target gene. TOM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TOM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOM1 BINDING SITE, designated SEQ ID:11987, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22421] Another function of VGAM492 is therefore inhibition of

Target of Myb1 (chicken) (TOM1, Accession NM\_005488). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOM1. LOC144667 (Accession XM\_096648) is another VGAM492 host target gene. LOC144667 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC144667, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144667 BINDING SITE, designated SEQ ID:40452, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22422] Another function of VGAM492 is therefore inhibition of LOC144667 (Accession XM\_096648). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144667. LOC220370 (Accession XM\_166943) is another VGAM492 host target gene. LOC220370 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC220370, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220370 BINDING SITE, designated SEQ ID:44599, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22423] Another function of VGAM492 is therefore inhibition of LOC220370 (Accession XM\_166943). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220370. LOC222255 (Accession XM\_168616) is another VGAM492 host target gene. LOC222255 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC222255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222255 BINDING SITE, designated SEQ ID:45272, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22424] Another function of VGAM492 is therefore inhibition of LOC222255 (Accession XM\_168616). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC222255. LOC253070 (Accession XM\_173088) is another VGAM492 host target gene. LOC253070 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253070, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253070 BINDING SITE, designated SEQ ID:46354, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22425] Another function of VGAM492 is therefore inhibition of LOC253070 (Accession XM\_173088). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253070. LOC257054 (Accession XM\_171010) is another VGAM492 host target gene. LOC257054 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257054, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257054 BINDING SITE, designated SEQ ID:45783, to the nucleotide sequence of VGAM492 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3203.

[22426] Another function of VGAM492 is therefore inhibition of LOC257054 (Accession XM\_171010). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257054. LOC93259 (Accession XM\_050105) is another VGAM492 host target gene. LOC93259 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC93259, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93259 BINDING SITE, designated SEQ ID:35558, to the nucleotide sequence of VGAM492 RNA, herein designated VGAM RNA, also designated SEQ ID:3203.

[22427] Another function of VGAM492 is therefore inhibition of LOC93259 (Accession XM\_050105). Accordingly, utilities of VGAM492 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93259. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 493 (VGAM493) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22428] VGAM493 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM493 was detected is described hereinabove with reference to Figs. 1–8.

[22429] VGAM493 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM493 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22430] VGAM493 gene encodes a VGAM493 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM493 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM493 precursor RNA is designated SEQ ID:479, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:479 is located at position 7135 relative to the genome of Hepatitis G Virus.

[22431] VGAM493 precursor RNA folds onto itself, forming

VGAM493 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22432] An enzyme complex designated DICER COMPLEX, `dices` the VGAM493 folded precursor RNA into VGAM493 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM493 RNA is designated SEQ ID:3204, and is provided hereinbelow with reference to the sequence listing part.

[22433] VGAM493 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM493 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM493 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.



[22434] VGAM493 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM493 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM493 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM493 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM493 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22435] The complementary binding of VGAM493 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM493 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM493 host target RNA into VGAM493 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22436] It is appreciated that VGAM493 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM493 host target genes. The mRNA of each one of this plurality of VGAM493 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM493 RNA, herein designated VGAM RNA, and which when bound by VGAM493 RNA causes inhibition of translation of respective one or more VGAM493 host target proteins.

[22437] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM493 gene, herein designated VGAM GENE, on one or more VGAM493 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22438] It is yet further appreciated that a function of VGAM493 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM493 correlate with, and may be deduced from, the identity of the host target genes which VGAM493 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22439] Nucleotide sequences of the VGAM493 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM493 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM493 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM493 are further described hereinbelow with reference to Table 1.

[22440] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM493 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM493 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22441] As mentioned hereinabove with reference to Fig. 1, a function of VGAM493 gene, herein designated VGAM is inhibition of expression of VGAM493 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM493 correlate with, and may be deduced from, the identity of the target genes which VGAM493 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22442] Eukaryotic Translation Initiation Factor 1A (EIF1A, Accession XM\_114147) is a VGAM493 host target gene. EIF1A BINDING SITE is HOST TARGET binding site found in the

5` untranslated region of mRNA encoded by EIF1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF1A BINDING SITE, designated SEQ ID:42726, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22443] A function of VGAM493 is therefore inhibition of Eukaryotic Translation Initiation Factor 1A (EIF1A, Accession XM\_114147), a gene which seems to be required for maximal rate of protein biosynthesis. Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF1A. The function of EIF1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM120.Fc Fragment of IgG, Low Affinity Ila, Receptor For (CD32) (FCGR2A, Accession XM\_086483) is another VGAM493 host target gene. FCGR2A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FCGR2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of FCGR2A BINDING SITE, designated SEQ ID:38701, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22444] Another function of VGAM493 is therefore inhibition of Fc Fragment of IgG, Low Affinity Ila, Receptor For (CD32) (FCGR2A, Accession XM\_086483), a gene which binds IgG immune complexes; member of the immunoglobulin superfamily. Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FCGR2A. The function of FCGR2A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM444. Ficolin (collagen/fibrinogen domain containing lectin) 2 (hucolin) (FCN2, Accession NM\_015839) is another VGAM493 host target gene. FCN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FCN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FCN2 BINDING SITE, designated SEQ ID:17952, to the nucleotide se-

quence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22445] Another function of VGAM493 is therefore inhibition of Ficolin (collagen/fibrinogen domain containing lectin) 2 (hucolin) (FCN2, Accession NM\_015839), a gene which is involved in phagocytosis of pathogens. Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FCN2. The function of FCN2 has been established by previous studies. Matsushita et al. (1996) reported the cloning and characterization of P35, a human lectin with collagen and fibrinogen domains. The P35 gene encodes ficolin 2 (FCN2). Endo et al. (1996) isolated genomic clones for P35 and a related gene shown to be identical to ficolin 1 (OMIM Ref. No. 601252). Endo et al. (1996) mapped both genes to 9q34 by fluorescence in situ hybridization.

[22446] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22447] Endo, Y.; Sato, Y.; Matsushita, M.; Fujita, T. : Cloning and characterization of the human lectin P35 gene and its related gene. Genomics 36: 515–521, 1996. ; and

- [22448] Matsushita, M.; Endo, Y.; Taira, S.; Sato, Y.; Fujita, T.; Ichikawa, N.; Nakata, M.; Misuochi, T. : A novel human lectin with collagen- and fibrinogen-like domains which functions as an.
- [22449] Further studies establishing the function and utilities of FCN2 are found in John Hopkins OMIM database record ID 601624, and in cited publications numbered 9383 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphorylase, Glycogen; Brain (PYGB, Accession NM\_002862) is another VGAM493 host target gene. PYGB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PYGB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PYGB BINDING SITE, designated SEQ ID:8766, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.
- [22450] Another function of VGAM493 is therefore inhibition of Phosphorylase, Glycogen; Brain (PYGB, Accession NM\_002862). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clini-



cal conditions associated with PYGB. Solute Carrier Family 22 (organic cation transporter), Member 5 (SLC22A5, Accession NM\_003060) is another VGAM493 host target gene. SLC22A5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SLC22A5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC22A5 BINDING SITE, designated SEQ ID:9025, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22451] Another function of VGAM493 is therefore inhibition of Solute Carrier Family 22 (organic cation transporter), Member 5 (SLC22A5, Accession NM\_003060). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC22A5. Solute Carrier Family 9 (sodium/hydrogen exchanger), Isoform 6 (SLC9A6, Accession NM\_006359) is another VGAM493 host target gene. SLC9A6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC9A6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC9A6 BINDING SITE, designated SEQ ID:13054, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22452] Another function of VGAM493 is therefore inhibition of Solute Carrier Family 9 (sodium/hydrogen exchanger), Isoform 6 (SLC9A6, Accession NM\_006359), a gene which is involved electroneutral exchange of protons for  $\text{Na}^+$  and  $\text{K}^+$  across the mitochondrial inner membrane. Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC9A6. The function of SLC9A6 has been established by previous studies. By searching sequence databases for proteins with sequence similarity to the *S. cerevisiae* mitochondrial sodium/hydrogen exchanger Nha2, Numata et al. (1998) identified the deduced protein product of the KIAA0267 cDNA (Nagase et al., 1996), SLC9A6. The KIAA0267-encoded protein shares 30% amino acid sequence identity with *S. cerevisiae* Nha2, and approximately 20 to 24% identity with the mammalian NHE isoforms NHE1 to NHE5 (see OMIM Ref. No. SLC9A5; 600477). Numata et al. (1998), who concluded that the

KIAA0267 cDNA lacks 5-prime coding sequence, isolated a human cDNA containing the complete coding sequence of SLC9A6, which they called NHE6. The deduced 669-amino acid SLC9A6 protein has 12 putative membrane-spanning segments within the N-terminal region, and a hydrophilic C terminus, similar to the topologies predicted for other NHEs. In addition, SLC9A6 has a putative mitochondrial inner membrane targeting signal at its N terminus. Northern blot analysis detected an approximately 5.5-kb SLC9A6 transcript that was ubiquitously expressed, with the most abundant expression in mitochondrion-rich tissues such as brain, skeletal muscle, and heart. Fluorescence microscopy suggested that SLC9A6 localizes to mitochondria. Numata et al. (1998) deleted the *S. cerevisiae* NHA2 gene by homologous disruption and found that benzamil-inhibitable, acid-activated sodium uptake into mitochondria was abolished in the mutant strain. The mutant strain also showed retarded growth on nonfermentable carbon sources and severely reduced survival during the stationary phase of the cell cycle compared with the parental strain, consistent with a defect in aerobic metabolism. The authors suggested that Nha2 and SLC9A6 are homologous sodium/hydrogen ex-

changers that are important for mitochondrial function.

[22453] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22454] Nagase, T.; Seki, N.; Ishikawa, K.; Ohira, M.; Kwarabayasi, Y.; Ohara, O.; Tanaka, A.; Kotani, H.; Miyajima, N.; Nomura, N. : Prediction of the coding sequences of unidentified human genes. VI. The coding sequences of 80 new genes (KIAA0201–KIAA0280) deduced by analysis of cDNA clones from cell line KG–1 and brain. DNA Res. 3: 321–329, 1996. Note: Supplement: DNA Res. 3: 341–354, 1996. ; and

[22455] Numata, M.; Petrecca, K.; Lake, N.; Orlowski, J. : Identification of a mitochondrial Na<sup>+</sup>/H<sup>+</sup> exchanger. J. Biol. Chem. 273: 6951–6959, 1998.

[22456] Further studies establishing the function and utilities of SLC9A6 are found in John Hopkins OMIM database record ID 300231, and in cited publications numbered 9011–9012 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SRGAP1 (Accession XM\_051143) is another VGAM493 host target gene. SRGAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

SRGAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRGAP1 BINDING SITE, designated SEQ ID:35756, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22457] Another function of VGAM493 is therefore inhibition of SRGAP1 (Accession XM\_051143). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRGAP1. Transient Receptor Potential Cation Channel, Subfamily C, Member 6 (TRPC6, Accession NM\_004621) is another VGAM493 host target gene. TRPC6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPC6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPC6 BINDING SITE, designated SEQ ID:10981, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22458] Another function of VGAM493 is therefore inhibition of

Transient Receptor Potential Cation Channel, Subfamily C, Member 6 (TRPC6, Accession NM\_004621), a gene which has calcium channel activity. Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPC6. The function of TRPC6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM25. Chromosome 7 Open Reading Frame 13 (C7orf13, Accession NM\_032625) is another VGAM493 host target gene. C7orf13 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C7orf13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C7orf13 BINDING SITE, designated SEQ ID:26344, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22459] Another function of VGAM493 is therefore inhibition of Chromosome 7 Open Reading Frame 13 (C7orf13, Accession NM\_032625). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with C7orf13. DKFZp547E052 (Accession NM\_032276) is another VGAM493 host target gene. DKFZp547E052 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547E052, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547E052 BINDING SITE, designated SEQ ID:26032, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22460] Another function of VGAM493 is therefore inhibition of DKFZp547E052 (Accession NM\_032276). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547E052. DKFZP761I2123 (Accession NM\_031449) is another VGAM493 host target gene. DKFZP761I2123 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP761I2123, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP761I2123 BINDING SITE,

designated SEQ ID:25464, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22461] Another function of VGAM493 is therefore inhibition of DKFZP761I2123 (Accession NM\_031449). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP761I2123. FLJ14082 (Accession NM\_025024) is another VGAM493 host target gene. FLJ14082 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14082, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14082 BINDING SITE, designated SEQ ID:24608, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22462] Another function of VGAM493 is therefore inhibition of FLJ14082 (Accession NM\_025024). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14082. FLJ22169 (Accession NM\_024085) is another VGAM493 host target gene. FLJ22169 BINDING SITE is HOST TARGET



binding site found in the 5' untranslated region of mRNA encoded by FLJ22169, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22169 BINDING SITE, designated SEQ ID:23524, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22463] Another function of VGAM493 is therefore inhibition of FLJ22169 (Accession NM\_024085). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22169. KIAA0133 (Accession NM\_014777) is another VGAM493 host target gene. KIAA0133 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0133, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0133 BINDING SITE, designated SEQ ID:16609, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22464] Another function of VGAM493 is therefore inhibition of

KIAA0133 (Accession NM\_014777). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0133. KIAA0152 (Accession NM\_014730) is another VGAM493 host target gene. KIAA0152 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0152, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0152 BINDING SITE, designated SEQ ID:16341, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22465] Another function of VGAM493 is therefore inhibition of KIAA0152 (Accession NM\_014730). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0152. KIAA1858 (Accession XM\_040592) is another VGAM493 host target gene. KIAA1858 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1858, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1858 BINDING SITE, designated SEQ ID:33329, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22466] Another function of VGAM493 is therefore inhibition of KIAA1858 (Accession XM\_040592). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1858. Low Density Lipoprotein-related Protein 1B (deleted in tumors) (LRP1B, Accession NM\_018557) is another VGAM493 host target gene. LRP1B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LRP1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRP1B BINDING SITE, designated SEQ ID:20641, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22467] Another function of VGAM493 is therefore inhibition of Low Density Lipoprotein-related Protein 1B (deleted in tumors) (LRP1B, Accession NM\_018557). Accordingly, utilities of VGAM493 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with LRP1B. Phosphatidylinositol Glycan, Class Q (PIGQ, Accession NM\_004204) is another VGAM493 host target gene. PIGQ BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIGQ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIGQ BINDING SITE, designated SEQ ID:10399, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22468] Another function of VGAM493 is therefore inhibition of Phosphatidylinositol Glycan, Class Q (PIGQ, Accession NM\_004204). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIGQ. Syntaphilin (SNPH, Accession NM\_014723) is another VGAM493 host target gene. SNPH BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SNPH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNPH BINDING SITE, designated SEQ ID:16302,

to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22469] Another function of VGAM493 is therefore inhibition of Syntaphilin (SNPH, Accession NM\_014723). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNPH. Thioesterase, Adipose Associated (THEA, Accession XM\_038922) is another VGAM493 host target gene. THEA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by THEA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of THEA BINDING SITE, designated SEQ ID:32950, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22470] Another function of VGAM493 is therefore inhibition of Thioesterase, Adipose Associated (THEA, Accession XM\_038922). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with THEA. LOC115110 (Accession XM\_049825) is another VGAM493 host target gene. LOC115110 BINDING SITE is HOST TARGET binding

site found in the 5` untranslated region of mRNA encoded by LOC115110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115110 BINDING SITE, designated SEQ ID:35513, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22471] Another function of VGAM493 is therefore inhibition of LOC115110 (Accession XM\_049825). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115110. LOC147138 (Accession XM\_085717) is another VGAM493 host target gene. LOC147138 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC147138, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147138 BINDING SITE, designated SEQ ID:38309, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22472] Another function of VGAM493 is therefore inhibition of

LOC147138 (Accession XM\_085717). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147138. LOC151121 (Accession XM\_087102) is another VGAM493 host target gene. LOC151121 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151121, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151121 BINDING SITE, designated SEQ ID:39053, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22473] Another function of VGAM493 is therefore inhibition of LOC151121 (Accession XM\_087102). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151121. LOC157280 (Accession XM\_058301) is another VGAM493 host target gene. LOC157280 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157280, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC157280 BINDING SITE, designated SEQ ID:36592, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22474] Another function of VGAM493 is therefore inhibition of LOC157280 (Accession XM\_058301). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157280. LOC158857 (Accession XM\_098997) is another VGAM493 host target gene. LOC158857 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158857, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158857 BINDING SITE, designated SEQ ID:42032, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22475] Another function of VGAM493 is therefore inhibition of LOC158857 (Accession XM\_098997). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158857. LOC159049 (Accession XM\_099020) is an-



other VGAM493 host target gene. LOC159049 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC159049, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC159049 BINDING SITE, designated SEQ ID:42058, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22476] Another function of VGAM493 is therefore inhibition of LOC159049 (Accession XM\_099020). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC159049. LOC170261 (Accession XM\_093214) is another VGAM493 host target gene. LOC170261 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC170261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170261 BINDING SITE, designated SEQ ID:40183, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22477] Another function of VGAM493 is therefore inhibition of LOC170261 (Accession XM\_093214). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170261. LOC205952 (Accession XM\_120685) is another VGAM493 host target gene. LOC205952 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC205952, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC205952 BINDING SITE, designated SEQ ID:43611, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22478] Another function of VGAM493 is therefore inhibition of LOC205952 (Accession XM\_120685). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC205952. LOC221756 (Accession XM\_166394) is another VGAM493 host target gene. LOC221756 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221756, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221756 BINDING SITE, designated SEQ ID:44242, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22479] Another function of VGAM493 is therefore inhibition of LOC221756 (Accession XM\_166394). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221756. LOC255448 (Accession XM\_170623) is another VGAM493 host target gene. LOC255448 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255448, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255448 BINDING SITE, designated SEQ ID:45402, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22480] Another function of VGAM493 is therefore inhibition of LOC255448 (Accession XM\_170623). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC255448. LOC256586 (Accession XM\_170759) is another VGAM493 host target gene. LOC256586 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256586, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256586 BINDING SITE, designated SEQ ID:45513, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22481] Another function of VGAM493 is therefore inhibition of LOC256586 (Accession XM\_170759). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256586. LOC257051 (Accession XM\_172800) is another VGAM493 host target gene. LOC257051 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257051, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257051 BINDING SITE, designated SEQ ID:46083, to the nucleotide sequence of VGAM493 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3204.

[22482] Another function of VGAM493 is therefore inhibition of LOC257051 (Accession XM\_172800). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257051. LOC91344 (Accession XM\_037782) is another VGAM493 host target gene. LOC91344 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91344, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91344 BINDING SITE, designated SEQ ID:32678, to the nucleotide sequence of VGAM493 RNA, herein designated VGAM RNA, also designated SEQ ID:3204.

[22483] Another function of VGAM493 is therefore inhibition of LOC91344 (Accession XM\_037782). Accordingly, utilities of VGAM493 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91344. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 494 (VGAM494) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22484] VGAM494 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM494 was detected is described hereinabove with reference to Figs. 1–8.

[22485] VGAM494 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM494 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22486] VGAM494 gene encodes a VGAM494 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM494 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM494 precursor RNA is designated SEQ ID:480, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:480 is located at position 4566 relative to the genome of Hepatitis G Virus.

[22487] VGAM494 precursor RNA folds onto itself, forming

VGAM494 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22488] An enzyme complex designated DICER COMPLEX, `dices` the VGAM494 folded precursor RNA into VGAM494 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM494 RNA is designated SEQ ID:3205, and is provided hereinbelow with reference to the sequence listing part.

[22489] VGAM494 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM494 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM494 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22490] VGAM494 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM494 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM494 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM494 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM494 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example



only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22491] The complementary binding of VGAM494 RNA, herein designated VGAM RNA, to host target binding sites on VGAM494 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM494 host target RNA into VGAM494 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22492] It is appreciated that VGAM494 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM494 host target genes. The mRNA of each one of this plurality of VGAM494 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM494 RNA, herein designated VGAM RNA, and which when bound by VGAM494 RNA causes inhibition of translation of respective one or more VGAM494 host target proteins.

[22493] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM494 gene, herein designated VGAM GENE, on one or more VGAM494 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22494] It is yet further appreciated that a function of VGAM494 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM494 correlate with, and may be deduced from, the identity of the host target genes which VGAM494 binds and inhibits, and the

function of these host target genes, as elaborated herein–below.

[22495] Nucleotide sequences of the VGAM494 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM494 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM494 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM494 are further described hereinbelow with reference to Table 1.

[22496] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM494 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM494 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22497] As mentioned hereinabove with reference to Fig. 1, a function of VGAM494 gene, herein designated VGAM is inhibition of expression of VGAM494 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM494 correlate with, and may be deduced from, the identity of the target genes which VGAM494 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[22498] ATPase, Class VI, Type 11A (ATP11A, Accession XM\_085028) is a VGAM494 host target gene. ATP11A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ATP11A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP11A BINDING SITE, designated SEQ ID:37801, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22499] A function of VGAM494 is therefore inhibition of ATPase, Class VI, Type 11A (ATP11A, Accession XM\_085028). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP11A. ATPase, Cu++ Transporting, Alpha Polypeptide (Menkes syndrome) (ATP7A, Accession NM\_000052) is another VGAM494 host target gene. ATP7A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ATP7A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of ATP7A BINDING SITE, designated SEQ ID:5497, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22500] Another function of VGAM494 is therefore inhibition of ATPase, Cu<sup>++</sup> Transporting, Alpha Polypeptide (Menkes syndrome) (ATP7A, Accession NM\_000052). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP7A. Bullous Pemphigoid Antigen 1, 230/240kDa (BPAG1, Accession NM\_015548) is another VGAM494 host target gene. BPAG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BPAG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BPAG1 BINDING SITE, designated SEQ ID:17809, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22501] Another function of VGAM494 is therefore inhibition of Bullous Pemphigoid Antigen 1, 230/240kDa (BPAG1, Accession NM\_015548), a gene which plays a role in cross-linking actin to other cytoskeletal proteins, binds to mi-

crotubules. Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BPAG1. The function of BPAG1 has been established by previous studies. Sensory neurodegeneration occurs in mice defective in Bpag1, a gene encoding cytoskeletal linker proteins capable of anchoring neuronal intermediate filaments to actin cytoskeleton. While Bpag1 null mice fail to anchor neurofilaments (NFs), Bpag1/NF null mice still degenerate in the absence of NFs. Yang et al. (1999) reported a novel BPAG1 neural splice form that lacks the actin-binding domain and instead binds and stabilizes microtubules. This interaction is functionally important; in mice and in vitro, neurons lacking BPAG1 displayed short, disorganized, and unstable microtubules defective in axonal transport. BPAG1 neural isoforms represent microtubule-associated proteins that when absent lead to devastating consequences. Moreover, BPAG1 can functionally account for the extraordinary stability of axonal microtubules necessary for transport over long distances. Its isoforms interconnect all 3 cytoskeletal networks, a feature apparently central to neuronal survival. Animal model experiments lend further support to the function of BPAG1. BPAG1 is made by stratified squa-

mous epithelia, where it localizes to the inner surface of specialized integrin-mediated adherens junctions (hemidesmosomes). Guo et al. (1995) explored the function of BPAG1 and its relationship to bullous pemphigoid by targeting the knockout of the Bpag1 gene in mice. Hemidesmosomes were otherwise normal but they lacked the inner plate and had no cytoskeleton attached. Though not affecting cell growth or adhesion to substrate, this change compromised mechanical integrity and influenced migration. Unexpectedly, the mice also developed severe dystonia and sensory nerve degeneration typical of homozygous dystonia musculorum (dt/dt) mice. Guo et al. (1995) showed that the Bpag1 gene is defective in at least 1 strain of mice with spontaneous homozygous dystonia musculorum. As indicated elsewhere, a human homolog of the dystonia musculorum gene (OMIM Ref. No. 600088) has been mapped to 6p12, the same region as the BPAG1 gene. The dt/dt locus is on mouse chromosome 1 in the same region as the Bpag1 locus. Guo et al. (1995) discussed the evidence that they may one and the same. Brown et al. (1995) cloned a candidate dt gene, called dystonin, that is predominantly expressed in the dorsal root ganglia and other sites of neurodegeneration in dt

mice. They showed that the dystonin gene encodes an N-terminal actin-binding domain and a C-terminal portion comprised of the bullous pemphigoid antigen-1 protein; dt and bpag1 are part of the same transcription unit which is partially deleted in a transgenic strain of mice that harbors an insertional mutation at the dt locus and in mice that carry a spontaneous dt mutation. They also demonstrated abnormal dystonin transcripts in a second dt mutant. Thus, they concluded that mutations in the dystonin gene are the primary genetic lesion in dt mice.

[22502] It is appreciated that the abovementioned animal model for BPAG1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[22503] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22504] Yang, Y.; Bauer, C.; Strasser, G.; Wollman, R.; Julien, J.-P.; Fuchs, E. : Integrators of the cytoskeleton that stabilize microtubules. Cell 98: 229-238, 1999. ; and

[22505] Guo, L.; Degenstein, L.; Dowling, J.; Yu, Q.-C.; Wollmann, R.; Perman, B.; Fuchs, E. : Gene targeting of BPAG1: abnormalities in mechanical strength and cell migration in



stratified ep.

[22506] Further studies establishing the function and utilities of BPAG1 are found in John Hopkins OMIM database record ID 113810, and in cited publications numbered 4079–4090 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. EphA8 (EPHA8, Accession NM\_020526) is another VGAM494 host target gene. EPHA8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPHA8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPHA8 BINDING SITE, designated SEQ ID:21742, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22507] Another function of VGAM494 is therefore inhibition of EphA8 (EPHA8, Accession NM\_020526), a gene which Eph-related receptor tyrosine kinase A8. Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPHA8. The function of EPHA8 has been established by previous studies. See EPH (EPHA1; 179610) for back–

ground on Eph receptors and their ligands, the ephrins. Chan and Watt (1991) identified human and rat DNAs encoding 2 novel members of the EPH subclass of putative receptor protein-tyrosine kinases. Rat cDNA clones encoding EEK (EPH- and ELK-related kinase) were isolated from a brain cDNA library probed with DNA encoding the kinase region of the insulin receptor-related receptor (INSRR; 147671). The EEK protein was predicted to contain all the amino acid residues conserved in the catalytic domains of protein-tyrosine kinases and was most similar to 2 putative receptor protein-tyrosine kinases of the EPH subclass, ELK (EPHB1; 600600) and EPH, showing 69 and 57% identity, respectively. Human genomic DNAs, encoding part of EEK as well as another putative protein tyrosine kinase most similar to ELK (90%) and symbolized ERK (EPHB2; 600997) for ELK-related kinase, were isolated and partially characterized. The novel identity of these 2 EPH-family genes was further supported by Southern blot analysis and localization to human chromosome 1. In Northern blot analysis of rat RNA, DNAs encoding rat EEK and human ERK hybridized to transcripts most abundant in brain and lung, respectively. These 2 new members of the EPH subclass of receptor protein-tyrosine kinases, EEK

and ERK, may therefore have tissue-specific functions distinct from those of the other EPH family members. Animal model experiments lend further support to the function of EPHA8. Park et al. (1997) generated mice homozygous for a mutation that disrupts the gene encoding EPHA8, a member of the Eph family of tyrosine proteinase receptors. EphA8  $-/-$  mice developed to term, were fertile, and did not display obvious anatomical or physiologic defects.

[22508] It is appreciated that the abovementioned animal model for EPHA8 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[22509] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22510] Chan, J.; Watt, V. M. : Eek and erk, new members of the eph subclass of receptor protein-tyrosine kinases. *Oncogene* 6: 1057-1061, 1991. ; and

[22511] Park, S.; Frisen, J.; Barbacid, M. : Aberrant axonal projections in mice lacking EphA8 (Eek) tyrosine protein kinase receptors. *EMBO J.* 16: 3106-3114, 1997.

[22512] Further studies establishing the function and utilities of EPHA8 are found in John Hopkins OMIM database record

ID 176945, and in cited publications numbered 12700–12701 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. WD Repeat Domain 1 (WDR1, Accession NM\_017491) is another VGAM494 host target gene. WDR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WDR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WDR1 BINDING SITE, designated SEQ ID:18956, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22513] Another function of VGAM494 is therefore inhibition of WD Repeat Domain 1 (WDR1, Accession NM\_017491). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WDR1. FLJ10781 (Accession NM\_018215) is another VGAM494 host target gene. FLJ10781 BINDING SITE1 and FLJ10781 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ10781, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BIND-

ING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10781 BINDING SITE1 and FLJ10781 BINDING SITE2, designated SEQ ID:20138 and SEQ ID:20131 respectively, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22514] Another function of VGAM494 is therefore inhibition of FLJ10781 (Accession NM\_018215). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10781. KIAA0450 (Accession NM\_014638) is another VGAM494 host target gene. KIAA0450 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0450, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0450 BINDING SITE, designated SEQ ID:16025, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22515] Another function of VGAM494 is therefore inhibition of KIAA0450 (Accession NM\_014638). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0450. KIAA1492 (Accession XM\_035312) is another VGAM494 host target gene. KIAA1492 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1492, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1492 BINDING SITE, designated SEQ ID:32226, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22516] Another function of VGAM494 is therefore inhibition of KIAA1492 (Accession XM\_035312). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1492. Ras and Rab Interactor 3 (RIN3, Accession NM\_024832) is another VGAM494 host target gene. RIN3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RIN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RIN3 BINDING SITE, designated SEQ ID:24229, to the nu-

cleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22517] Another function of VGAM494 is therefore inhibition of Ras and Rab Interactor 3 (RIN3, Accession NM\_024832). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RIN3. LOC115110 (Accession XM\_049825) is another VGAM494 host target gene. LOC115110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115110 BINDING SITE, designated SEQ ID:35512, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22518] Another function of VGAM494 is therefore inhibition of LOC115110 (Accession XM\_049825). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115110. LOC196500 (Accession XM\_113734) is another VGAM494 host target gene. LOC196500 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC196500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196500 BINDING SITE, designated SEQ ID:42384, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22519] Another function of VGAM494 is therefore inhibition of LOC196500 (Accession XM\_113734). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196500. LOC197287 (Accession XM\_027541) is another VGAM494 host target gene. LOC197287 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197287, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197287 BINDING SITE, designated SEQ ID:30520, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22520] Another function of VGAM494 is therefore inhibition of LOC197287 (Accession XM\_027541). Accordingly, utilities



of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197287. LOC91782 (Accession XM\_040612) is another VGAM494 host target gene. LOC91782 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91782, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91782 BINDING SITE, designated SEQ ID:33335, to the nucleotide sequence of VGAM494 RNA, herein designated VGAM RNA, also designated SEQ ID:3205.

[22521] Another function of VGAM494 is therefore inhibition of LOC91782 (Accession XM\_040612). Accordingly, utilities of VGAM494 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91782. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 495 (VGAM495) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22522] VGAM495 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM495 was detected is described hereinabove with reference to Figs. 1–8.

[22523] VGAM495 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis G Virus. VGAM495 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22524] VGAM495 gene encodes a VGAM495 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM495 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM495 precursor RNA is designated SEQ ID:481, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:481 is located at position 3092 relative to the genome of Hepatitis G Virus.

[22525] VGAM495 precursor RNA folds onto itself, forming VGAM495 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22526] An enzyme complex designated DICER COMPLEX, `dices` the VGAM495 folded precursor RNA into VGAM495 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM495 RNA is designated SEQ ID:3206, and is provided hereinbelow with reference to the sequence listing part.

[22527] VGAM495 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM495 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM495 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[22528] VGAM495 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM495 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM495 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM495 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM495 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22529] The complementary binding of VGAM495 RNA, herein designated VGAM RNA, to host target binding sites on VGAM495 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM495 host target RNA into VGAM495 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22530] It is appreciated that VGAM495 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM495 host target genes. The mRNA of each one of this plurality of VGAM495 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM495 RNA, herein designated VGAM RNA, and which when bound by VGAM495 RNA causes inhibition of translation of respective one or more VGAM495 host target proteins.

[22531] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM495 gene, herein designated VGAM GENE, on one or more VGAM495 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22532] It is yet further appreciated that a function of VGAM495 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM495 include diagnosis, prevention and treatment of viral infection by Hepatitis G Virus. Specific functions, and accordingly utilities, of VGAM495 correlate with, and may be deduced from, the identity of the host target genes which VGAM495 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22533] Nucleotide sequences of the VGAM495 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM495 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM495 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM495 are further  
described hereinbelow with reference to Table 1.

[22534] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM495 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM495 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[22535] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM495 gene, herein designated VGAM is  
inhibition of expression of VGAM495 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM495 correlate with, and may be deduced  
from, the identity of the target genes which VGAM495  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[22536] FLJ22056 (Accession NM\_022489) is a VGAM495 host tar-  
get gene. FLJ22056 BINDING SITE is HOST TARGET binding

site found in the 5` untranslated region of mRNA encoded by FLJ22056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22056 BINDING SITE, designated SEQ ID:22867, to the nucleotide sequence of VGAM495 RNA, herein designated VGAM RNA, also designated SEQ ID:3206.

[22537] A function of VGAM495 is therefore inhibition of FLJ22056 (Accession NM\_022489). Accordingly, utilities of VGAM495 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22056. FLJ30567 (Accession NM\_145022) is another VGAM495 host target gene. FLJ30567 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ30567, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ30567 BINDING SITE, designated SEQ ID:29631, to the nucleotide sequence of VGAM495 RNA, herein designated VGAM RNA, also designated SEQ ID:3206.

[22538] Another function of VGAM495 is therefore inhibition of



FLJ30567 (Accession NM\_145022). Accordingly, utilities of VGAM495 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ30567. LOC150142 (Accession XM\_086791) is another VGAM495 host target gene. LOC150142 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150142 BINDING SITE, designated SEQ ID:38855, to the nucleotide sequence of VGAM495 RNA, herein designated VGAM RNA, also designated SEQ ID:3206.

[22539] Another function of VGAM495 is therefore inhibition of LOC150142 (Accession XM\_086791). Accordingly, utilities of VGAM495 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150142. LOC199858 (Accession XM\_114040) is another VGAM495 host target gene. LOC199858 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199858, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC199858 BINDING SITE, designated SEQ ID:42642, to the nucleotide sequence of VGAM495 RNA, herein designated VGAM RNA, also designated SEQ ID:3206.

[22540] Another function of VGAM495 is therefore inhibition of LOC199858 (Accession XM\_114040). Accordingly, utilities of VGAM495 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199858. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 496 (VGAM496) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22541] VGAM496 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM496 was detected is described hereinabove with reference to Figs. 1–8.

[22542] VGAM496 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 7. VGAM496 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[22543] VGAM496 gene encodes a VGAM496 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM496 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM496 precursor RNA is designated SEQ ID:482, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:482 is located at position 58821 relative to the genome of Human Herpesvirus 7.

[22544] VGAM496 precursor RNA folds onto itself, forming VGAM496 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22545] An enzyme complex designated DICER COMPLEX, `dices` the VGAM496 folded precursor RNA into VGAM496 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM496 RNA is designated SEQ ID:3207, and is provided hereinbelow with reference to the sequence listing part.

[22546] VGAM496 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM496 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM496 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22547] VGAM496 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM496 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM496 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM496 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM496 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22548] The complementary binding of VGAM496 RNA, herein designated VGAM RNA, to host target binding sites on VGAM496 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM496 host target RNA into VGAM496 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22549] It is appreciated that VGAM496 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM496 host target genes. The mRNA of each one of this plurality of VGAM496 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM496 RNA, herein designated VGAM RNA, and which when bound by VGAM496 RNA causes inhibition of translation of respective one or more VGAM496 host target proteins.

[22550] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM496 gene, herein designated VGAM GENE, on one or more VGAM496 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22551] It is yet further appreciated that a function of VGAM496 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 7. Specific functions, and accordingly utilities, of VGAM496 correlate with, and may be deduced from, the identity of the host target genes which VGAM496 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22552] Nucleotide sequences of the VGAM496 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM496 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM496 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM496 are further described hereinbelow with reference to Table 1.

[22553] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM496 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM496 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22554] As mentioned hereinabove with reference to Fig. 1, a function of VGAM496 gene, herein designated VGAM is inhibition of expression of VGAM496 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM496 correlate with, and may be deduced from, the identity of the target genes which VGAM496 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22555] Acyl-Coenzyme A Dehydrogenase, Short/branched Chain (ACADSB, Accession NM\_001609) is a VGAM496 host target gene. ACADSB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ACADSB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACADSB BINDING SITE, designated SEQ ID:7316, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ



ID:3207.

[22556] A function of VGAM496 is therefore inhibition of Acyl-Coenzyme A Dehydrogenase, Short/branched Chain (ACADSB, Accession NM\_001609). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACADSB. Collagen-like Tail Subunit (single strand of homotrimer) of Asymmetric Acetylcholinesterase (COLQ, Accession NM\_005677) is another VGAM496 host target gene. COLQ BINDING SITE1 through COLQ BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by COLQ, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COLQ BINDING SITE1 through COLQ BINDING SITE6, designated SEQ ID:12233, SEQ ID:27865, SEQ ID:27859, SEQ ID:27853, SEQ ID:27862 and SEQ ID:27856 respectively, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22557] Another function of VGAM496 is therefore inhibition of Collagen-like Tail Subunit (single strand of homotrimer) of Asymmetric Acetylcholinesterase (COLQ, Accession

NM\_005677). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COLQ. UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1 (GalNAc-T1) (GALNT1, Accession NM\_020474) is another VGAM496 host target gene. GALNT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GALNT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GALNT1 BINDING SITE, designated SEQ ID:21722, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22558] Another function of VGAM496 is therefore inhibition of UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 1 (GalNAc-T1) (GALNT1, Accession NM\_020474), a gene which transfers an N-acetyl galactosamine (GalNAc) to a serine or threonine residue in the first step of O-linked oligosaccharide biosynthesis. Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical

cal conditions associated with GALNT1. The function of GALNT1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM120.LFG (Accession XM\_084780) is another VGAM496 host target gene. LFG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LFG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LFG BINDING SITE, designated SEQ ID:37693, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22559] Another function of VGAM496 is therefore inhibition of LFG (Accession XM\_084780). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LFG. Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005) is another VGAM496 host target gene. PCDHA9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA9, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA9 BINDING SITE, designated SEQ ID:15208, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22560] Another function of VGAM496 is therefore inhibition of Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005), a gene which is a calcium-dependent cell-adhesion protein. Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA9. The function of PCDHA9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM71. Retinitis Pigmentosa 2 (X-linked recessive) (RP2, Accession NM\_006915) is another VGAM496 host target gene. RP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RP2 BINDING SITE, designated SEQ ID:13789, to the nucleotide sequence of VGAM496 RNA, herein designated

VGAM RNA, also designated SEQ ID:3207.

[22561] Another function of VGAM496 is therefore inhibition of Retinitis Pigmentosa 2 (X-linked recessive) (RP2, Accession NM\_006915). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RP2. SRGAP1 (Accession XM\_051143) is another VGAM496 host target gene. SRGAP1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SRGAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRGAP1 BINDING SITE, designated SEQ ID:35759, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22562] Another function of VGAM496 is therefore inhibition of SRGAP1 (Accession XM\_051143). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRGAP1. Surfeit 4 (SURF4, Accession NM\_033161) is another VGAM496 host target gene. SURF4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by SURF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SURF4 BINDING SITE, designated SEQ ID:27011, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22563] Another function of VGAM496 is therefore inhibition of Surfeit 4 (SURF4, Accession NM\_033161), a gene which is a conserved integral membrane protein containing multiple putative transmembrane regions. Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SURF4. The function of SURF4 has been established by previous studies. Using PCR with primers based on the sequence of mouse Surf4 to screen a HeLa cell cDNA library, Reeves and Fried (1995) obtained a cDNA encoding human SURF4. The deduced 269-amino acid protein, which is 60% and 99% identical to the worm and mouse proteins, respectively, contains 7 transmembrane segments, a predicted luminal N terminus, multiple phosphorylation sites, and a double-lysine retrieval motif at the C terminus. Immunoblot analysis showed expression of a 30-kD

membrane protein. Immunofluorescence microscopy demonstrated cytoplasmic expression. Belden and Barlowe (2001) showed that Erv29, the yeast homolog of SURF4, is directly required for packaging glycosylated pro- $\alpha$ -factor (Gpaf) into COPII (see OMIM Ref. No. COPA; 601924) vesicles. Subcellular fractionation experiments indicated that Erv29 is equally distributed between endoplasmic reticulum (ER) and Golgi membranes. Increased expression of Erv29 in the ER alleviated the accumulation of Gpaf. Belden and Barlowe (2001) proposed that Erv29 binds to fully folded Gpaf and probably to other soluble secretory cargo in the ER, after which the Erv29-cargo complexes are packaged into COPII vesicles for transport to the Golgi complex. The authors noted that similar mechanisms have been postulated for ERGIC1 (LMAN1; 601567).

[22564] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22565] Belden, W. J.; Barlowe, C. : Role of Erv29p in collecting soluble secretory proteins into ER-derived transport vesicles. *Science* 294: 1528–1531, 2001. ; and

[22566] Reeves, J. E.; Fried, M. : The surf-4 gene encodes a novel

30 kDa integral membrane protein. Molec. Membr. Biol. 12: 201–208, 1995.

[22567] Further studies establishing the function and utilities of SURF4 are found in John Hopkins OMIM database record ID 185660, and in cited publications numbered 10458–10460 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ABLIM (Accession NM\_002313) is another VGAM496 host target gene. ABLIM BINDING SITE1 and ABLIM BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABLIM, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABLIM BINDING SITE1 and ABLIM BINDING SITE2, designated SEQ ID:8111 and SEQ ID:13544 respectively, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22568] Another function of VGAM496 is therefore inhibition of ABLIM (Accession NM\_002313). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABLIM. DKFZP761C169 (Accession XM\_042059) is another



VGAM496 host target gene. DKFZP761C169 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP761C169, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP761C169 BINDING SITE, designated SEQ ID:33679, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22569] Another function of VGAM496 is therefore inhibition of DKFZP761C169 (Accession XM\_042059). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP761C169. FLJ10737 (Accession NM\_018198) is another VGAM496 host target gene. FLJ10737 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10737, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10737 BINDING SITE, designated SEQ ID:20064, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22570] Another function of VGAM496 is therefore inhibition of FLJ10737 (Accession NM\_018198). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10737. FLJ11273 (Accession NM\_018374) is another VGAM496 host target gene. FLJ11273 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11273 BINDING SITE, designated SEQ ID:20394, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22571] Another function of VGAM496 is therefore inhibition of FLJ11273 (Accession NM\_018374). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11273. FLJ11710 (Accession NM\_024846) is another VGAM496 host target gene. FLJ11710 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11710, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

**BINDING SITE III.** Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11710 BINDING SITE, designated SEQ ID:24278, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22572] Another function of VGAM496 is therefore inhibition of FLJ11710 (Accession NM\_024846). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11710. FLJ20189 (Accession NM\_017704) is another VGAM496 host target gene. FLJ20189 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20189, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20189 BINDING SITE, designated SEQ ID:19280, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22573] Another function of VGAM496 is therefore inhibition of FLJ20189 (Accession NM\_017704). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20189.

FLJ20668 (Accession NM\_017923) is another VGAM496 host target gene. FLJ20668 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20668, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20668 BINDING SITE, designated SEQ ID:19589, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22574] Another function of VGAM496 is therefore inhibition of FLJ20668 (Accession NM\_017923). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20668. FLJ20694 (Accession NM\_017928) is another VGAM496 host target gene. FLJ20694 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20694, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20694 BINDING SITE, designated SEQ ID:19606, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3207.

[22575] Another function of VGAM496 is therefore inhibition of FLJ20694 (Accession NM\_017928). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20694. FXYD Domain Containing Ion Transport Regulator 3 (FXYD3, Accession NM\_005971) is another VGAM496 host target gene. FXYD3 BINDING SITE1 and FXYD3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FXYD3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FXYD3 BINDING SITE1 and FXYD3 BINDING SITE2, designated SEQ ID:12594 and SEQ ID:22437 respectively, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22576] Another function of VGAM496 is therefore inhibition of FXYD Domain Containing Ion Transport Regulator 3 (FXYD3, Accession NM\_005971). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FXYD3. KIAA0237 (Accession NM\_014747) is another VGAM496

host target gene. KIAA0237 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0237 BINDING SITE, designated SEQ ID:16456, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22577] Another function of VGAM496 is therefore inhibition of KIAA0237 (Accession NM\_014747). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0237. KIAA0435 (Accession NM\_014801) is another VGAM496 host target gene. KIAA0435 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0435, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0435 BINDING SITE, designated SEQ ID:16723, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22578] Another function of VGAM496 is therefore inhibition of KIAA0435 (Accession NM\_014801). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0435. KIAA1729 (Accession XM\_114418) is another VGAM496 host target gene. KIAA1729 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1729, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1729 BINDING SITE, designated SEQ ID:42948, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22579] Another function of VGAM496 is therefore inhibition of KIAA1729 (Accession XM\_114418). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1729. MGC10960 (Accession NM\_032653) is another VGAM496 host target gene. MGC10960 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC10960, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC10960 BINDING SITE, designated SEQ ID:26384, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22580] Another function of VGAM496 is therefore inhibition of MGC10960 (Accession NM\_032653). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10960. MGC2865 (Accession NM\_032375) is another VGAM496 host target gene. MGC2865 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2865, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2865 BINDING SITE, designated SEQ ID:26166, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22581] Another function of VGAM496 is therefore inhibition of MGC2865 (Accession NM\_032375). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



MGC2865. RAB39, Member RAS Oncogene Family (RAB39, Accession XM\_084662) is another VGAM496 host target gene. RAB39 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB39, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB39 BINDING SITE, designated SEQ ID:37647, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22582] Another function of VGAM496 is therefore inhibition of RAB39, Member RAS Oncogene Family (RAB39, Accession XM\_084662). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB39. T-cell Leukemia/lymphoma 6 (TCL6, Accession NM\_020552) is another VGAM496 host target gene. TCL6 BINDING SITE1 and TCL6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TCL6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of TCL6 BINDING SITE1 and TCL6 BINDING SITE2, designated SEQ ID:21767 and SEQ ID:21774 respectively, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22583] Another function of VGAM496 is therefore inhibition of T-cell Leukemia/lymphoma 6 (TCL6, Accession NM\_020552). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCL6. LOC127428 (Accession XM\_059144) is another VGAM496 host target gene. LOC127428 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC127428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127428 BINDING SITE, designated SEQ ID:36897, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22584] Another function of VGAM496 is therefore inhibition of LOC127428 (Accession XM\_059144). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC127428. LOC139331 (Accession XM\_066631) is another VGAM496 host target gene. LOC139331 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC139331, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC139331 BINDING SITE, designated SEQ ID:37341, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22585] Another function of VGAM496 is therefore inhibition of LOC139331 (Accession XM\_066631). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC139331. LOC147991 (Accession XM\_085993) is another VGAM496 host target gene. LOC147991 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147991, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147991 BINDING SITE, designated SEQ ID:38435, to the nucleotide sequence of VGAM496 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3207.

[22586] Another function of VGAM496 is therefore inhibition of LOC147991 (Accession XM\_085993). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147991. LOC149267 (Accession NM\_138480) is another VGAM496 host target gene. LOC149267 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149267, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149267 BINDING SITE, designated SEQ ID:28834, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22587] Another function of VGAM496 is therefore inhibition of LOC149267 (Accession NM\_138480). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149267. LOC162333 (Accession XM\_102591) is another VGAM496 host target gene. LOC162333 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC162333, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162333 BINDING SITE, designated SEQ ID:42141, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22588] Another function of VGAM496 is therefore inhibition of LOC162333 (Accession XM\_102591). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162333. LOC219673 (Accession XM\_167567) is another VGAM496 host target gene. LOC219673 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219673, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219673 BINDING SITE, designated SEQ ID:44695, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22589] Another function of VGAM496 is therefore inhibition of LOC219673 (Accession XM\_167567). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC219673. LOC221301 (Accession XM\_166308) is another VGAM496 host target gene. LOC221301 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221301 BINDING SITE, designated SEQ ID:44129, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22590] Another function of VGAM496 is therefore inhibition of LOC221301 (Accession XM\_166308). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221301. LOC221421 (Accession XM\_166428) is another VGAM496 host target gene. LOC221421 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221421, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221421 BINDING SITE, designated SEQ ID:44321, to

the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22591] Another function of VGAM496 is therefore inhibition of LOC221421 (Accession XM\_166428). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221421. LOC90321 (Accession XM\_030896) is another VGAM496 host target gene. LOC90321 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90321, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90321 BINDING SITE, designated SEQ ID:31212, to the nucleotide sequence of VGAM496 RNA, herein designated VGAM RNA, also designated SEQ ID:3207.

[22592] Another function of VGAM496 is therefore inhibition of LOC90321 (Accession XM\_030896). Accordingly, utilities of VGAM496 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90321. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 497 (VGAM497) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22593] VGAM497 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM497 was detected is described hereinabove with reference to Figs. 1-8.

[22594] VGAM497 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 7. VGAM497 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22595] VGAM497 gene encodes a VGAM497 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM497 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM497 precursor RNA is designated SEQ ID:483, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:483 is located at position 58211 relative to the genome of Human Herpesvirus 7.



[22596] VGAM497 precursor RNA folds onto itself, forming VGAM497 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22597] An enzyme complex designated DICER COMPLEX, `dices` the VGAM497 folded precursor RNA into VGAM497 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM497 RNA is designated SEQ ID:3208, and is provided hereinbelow with reference to the sequence listing part.

[22598] VGAM497 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM497 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM497 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22599] VGAM497 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM497 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM497 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM497 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM497 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22600] The complementary binding of VGAM497 RNA, herein designated VGAM RNA, to host target binding sites on VGAM497 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM497 host target RNA into VGAM497 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22601] It is appreciated that VGAM497 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM497 host target genes. The mRNA of each one of this plurality of VGAM497 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM497 RNA, herein designated VGAM RNA, and which when bound by VGAM497 RNA causes inhibition of translation of respective one or more VGAM497 host target proteins.

[22602] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM497 gene, herein designated VGAM GENE, on one or more VGAM497 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22603] It is yet further appreciated that a function of VGAM497 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 7. Specific functions, and accordingly utilities, of VGAM497 correlate with, and may be deduced from, the identity of the

host target genes which VGAM497 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22604] Nucleotide sequences of the VGAM497 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM497 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM497 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM497 are further described hereinbelow with reference to Table 1.

[22605] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM497 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM497 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22606] As mentioned hereinabove with reference to Fig. 1, a function of VGAM497 gene, herein designated VGAM is inhibition of expression of VGAM497 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM497 correlate with, and may be deduced from, the identity of the target genes which VGAM497

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22607] Amyloid Beta (A4) Precursor Protein (protease nexin-II, Alzheimer disease) (APP, Accession NM\_000484) is a VGAM497 host target gene. APP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APP BINDING SITE, designated SEQ ID:6092, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22608] A function of VGAM497 is therefore inhibition of Amyloid Beta (A4) Precursor Protein (protease nexin-II, Alzheimer disease) (APP, Accession NM\_000484). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APP. Bromodomain and PHD Finger Containing, 1 (BRPF1, Accession XM\_054520) is another VGAM497 host target gene. BRPF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BRPF1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BRPF1 BINDING SITE, designated SEQ ID:36175, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22609] Another function of VGAM497 is therefore inhibition of Bromodomain and PHD Finger Containing, 1 (BRPF1, Accession XM\_054520), a gene which has 6 zinc finger motifs and a bromodomain. Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BRPF1. The function of BRPF1 has been established by previous studies. Thompson et al. (1994) cloned a cDNA encoding a predicted 1,214-amino acid protein that they designated BR140. The BR140 protein, known also as peregrin, has 6 zinc finger motifs and a bromodomain. Thompson et al. (1994) found that BR140 migrates as a 150-kD protein on SDS-PAGE. Northern blots showed that BR140 is expressed ubiquitously. Western blots and immunohistochemistry revealed that BR140 is expressed at the highest level in testes and spermatogonia, and is localized within nuclei. Gregorini et al. (1996) noted that BR140 is very

similar in structure to 2 other zinc finger genes, AF10 (OMIM Ref. No. 602409) and AF17 (MLLT6; 600328) and suggested that they form a family of regulatory proteins. Gregorini et al. (1996) mapped the BR140 gene to 3p25–p26 by fluorescence in situ hybridization.

[22610] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22611] Gregorini, A.; Sahin, F. I.; Lillington, D. M.; Meerabux, J.; Saha, V.; McCullagh, P.; Bocci, M.; Menevse, S.; Papa, S.; Young, B. D. : Gene BR140, which is related to AF10 and AF17, maps to chromosome band 3p25. *Genes Chromosomes Cancer* 17: 269–272, 1996. ; and

[22612] Thompson, K. A.; Wang, B.; Argraves, W. S.; Giancotti, F. G.; Schranck, D. P.; Ruoslahti, E. : BR140, a novel zinc-finger protein with homology to the TAF250 subunit of TFIID. *Biochem.*

[22613] Further studies establishing the function and utilities of BRPF1 are found in John Hopkins OMIM database record ID 602410, and in cited publications numbered 6014–6015 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CAMP Responsive Element Binding Protein 1 (CREB1, Accession NM\_004379)



is another VGAM497 host target gene. CREB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CREB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CREB1 BINDING SITE, designated SEQ ID:10602, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22614] Another function of VGAM497 is therefore inhibition of CAMP Responsive Element Binding Protein 1 (CREB1, Accession NM\_004379), a gene which regulates expression of cAMP-inducible genes. Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CREB1. The function of CREB1 has been established by previous studies. Cyclic AMP (cAMP) second messenger pathways provide a chief means by which cellular growth, differentiation, and function can be influenced by extracellular signals. Following hormonal stimulation of a neuroendocrine cell, for example, increased cAMP levels activate cAMP-dependent protein kinase A, which phosphorylates 1 or more DNA-binding proteins. These in turn stimulate tran-

scription of an array of cAMP-responsive genes such as those for somatostatin (OMIM Ref. No. 182450), alpha-gonadotropin (OMIM Ref. No. 118850), proenkephalin (OMIM Ref. No. 131330) and FOS (OMIM Ref. No. 164810). All cAMP-responsive gene promoters have in common an 8-base enhancer known as the cAMP-response element (CRE) containing a conserved core sequence, 5-prime-TGACG-3-prime, first described in the somatostatin gene by Montminy et al. (1986). Montminy and Bilezikjian (1987) purified a 43-kD nuclear phosphoprotein, which binds to CRE with high affinity. Hoeffler et al. (1988) isolated cDNA clones for human CREB. CREB1 may be identical to activating transcription factor (ATF). By use of a cDNA probe for Southern blot analysis of genomic DNA from a panel of mouse/human somatic cell hybrids and for in situ hybridization, Taylor et al. (1990) mapped CREB1 to 2q32.3-q34. Taylor et al. (1990) speculated about the possible involvement of CREB1 in genetic disorders or cancer and pointed to the fact that TCL4 (OMIM Ref. No. 186860), a locus implicated in T-cell leukemia/lymphoma, is located at 2q34. Cole et al. (1992) demonstrated that the Creb-1 locus maps to the proximal region of mouse chromosome 1. The CREB gene was found to be

single copy in the mouse and well conserved through evolution. Barton et al. (1992) mapped the Creb-1 gene to mouse chromosome 1 by linkage studies. It was found to be approximately 1 cM distal to Cryg and 7 cM proximal to Vil. cAMP mediates the effects of TSH (OMIM Ref. No. 118850) by regulating thyroid follicular cell proliferation, differentiation, and function. To assess the functional importance of the cAMP response element-binding protein (CREB) in thyroid follicular cell regulation in vivo, Nguyen et al. (2000) targeted the expression of a dominant-negative CREB isoform to the thyroid glands of transgenic mice using a tissue-specific promoter. Transgenic mice exhibited severe growth retardation and primary hypothyroidism. Serum levels of TSH were elevated 8-fold above normal levels, and T4 and T3 levels were low. Ciliated thyroid epithelial cells were observed in the transgenic thyroid glands, suggesting a failure of follicular cell differentiation. Nguyen et al. (2000) concluded that these results demonstrate a critical role for CREB in thyroid growth, differentiation, and function in vivo. Animal model experiments lend further support to the function of CREB1. Kida et al. (2002) generated transgenic mice with an inducible and reversible CREB repressor by fusing CREB with a

ser133-to-ala mutation to a tamoxifen-dependent mutant of an estrogen receptor ligand-binding domain. They found that CREB is crucial for the consolidation of long-term conditioned fear memories, but not for encoding, storage, or retrieval of these memories. Their studies also showed that CREB is required for the stability of reactivated or retrieved conditioned fear memories. Although the transcriptional processes necessary for the stability of initial and reactivated memories differ, CREB was found to be required for both.

[22615] It is appreciated that the abovementioned animal model for CREB1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[22616] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22617] Barton, C. H.; Ajioka, J. W.; Roach, T. I. A.; Blackwell, J. M. : Mapping Creb-1 to chromosome 1 in the mouse. *Genomics* 14: 790-792, 1992. ; and

[22618] Kida, S.; Josselyn, S. A.; Pena de Ortiz, S.; Kogan, J. H.; Chevere, I.; Masushige, S.; Silva, A. J. : CREB required for the stability of new and reactivated fear memories. *Nature*

Neuros.

[22619] Further studies establishing the function and utilities of CREB1 are found in John Hopkins OMIM database record ID 123810, and in cited publications numbered 11851–11857, 1204 and 150–157 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Diacylglycerol Kinase, Beta 90kDa (DGKB, Accession XM\_166516) is another VGAM497 host target gene. DGKB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DGKB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGKB BINDING SITE, designated SEQ ID:44448, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22620] Another function of VGAM497 is therefore inhibition of Diacylglycerol Kinase, Beta 90kDa (DGKB, Accession XM\_166516), a gene which regulates the intracellular concentration of the second messenger diacylglycerol (DAG). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with DGKB. The function of DGKB has been established by previous studies. Diacylglycerol kinase (DGK) plays a key role in cellular processes by regulating the intracellular concentration of the second messenger diacylglycerol (DAG). For background information on the DGKs, see DGK-alpha (80-kD DGK; 125855). Goto and Kondo (1993) isolated rat brain cDNAs encoding a novel 90-kD DGK. The predicted 90-kD DGK protein was 58% identical to the rat 80-kD DGK. Both proteins contain EF-hand motifs, cysteine-rich zinc finger-like sequences, and putative ATP-binding sites. When expressed in mammalian cells, the 90-kD protein exhibited DGK activity. Northern blot analysis revealed that the 90-kD DGK was expressed as an approximately 6.2-kb transcript predominantly in brain. In situ hybridization to rat tissues indicated that the 90-kD DGK was expressed intensely in restricted brain regions such as the caudate putamen and olfactory tubercle. The pattern of expression was different from that of the 80-kD DGK, leading the authors to suggest that there are multiple DGK isozymes, each of which has a characteristic regional pattern of expression. By screening human brain cDNAs for those encoding proteins larger than 50 kD, Nagase et al. (1998) identified KIAA0718, a cDNA

encoding a human homolog of rat Dgkb. Using radiation hybrid analysis, they mapped the DGKB gene to chromosome 7.

[22621] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22622] Goto, K.; Kondo, H. : Molecular cloning and expression of a 90-kDa diacylglycerol kinase that predominantly localizes in neurons. Proc. Nat. Acad. Sci. 90: 7598–7602, 1993. ; and

[22623] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. XI. The c.

[22624] Further studies establishing the function and utilities of DGKB are found in John Hopkins OMIM database record ID 604070, and in cited publications numbered 63 and 7048 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ems1 Sequence (mammary tumor and squamous cell carcinoma-associated (p80/85 src substrate) (EMS1, Accession NM\_138565) is another VGAM497 host target gene. EMS1 BINDING SITE1 and EMS1 BINDING SITE2 are HOST TARGET

binding sites found in untranslated regions of mRNA encoded by EMS1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EMS1 BINDING SITE1 and EMS1 BINDING SITE2, designated SEQ ID:28868 and SEQ ID:11737 respectively, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22625] Another function of VGAM497 is therefore inhibition of Ems1 Sequence (mammary tumor and squamous cell carcinoma-associated (p80/85 src substrate) (EMS1, Accession NM\_138565), a gene which may contribute to the organization of cell structure. in transformed cells may contribute to cellular growth regulation and transformation. Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EMS1. The function of EMS1 has been established by previous studies. Amplification of the 11q13 region is frequently found in breast cancer and in squamous cell carcinomas of the head and neck. The known oncogenes within the amplified 11q13 region, INT2 (OMIM Ref. No. 164950) and FGF4 (OMIM Ref. No. 164980), are



rarely expressed in these tumors, indicating that another, hitherto unidentified gene or genes are involved in the unfavorable clinical course of disease associated with such amplification. To identify the gene or genes, Schuuring et al. (1992) constructed a cDNA library from a cell line with an 11q13 amplification and performed a differential cDNA cloning using labeled cDNAs from human squamous cell carcinoma cell lines with and without an 11q13 amplification. They isolated 2 cDNA clones, U21B31 and U21C8, which recognized genes amplified and overexpressed in cell lines harboring an 11q13 amplification. Sequence analysis of the U21C8 cDNA clone revealed no homology to known genes; they called this gene EMS1. The U21B31 cDNA clone corresponded to the 3-prime end of the PRAD1 protooncogene (OMIM Ref. No. 168461). Van Damme et al. (1997) stated that EMS1 is the human homolog of cortactin, an actin-binding protein involved in the restructuring of the cortical actin cytoskeleton. Cortactin is a substrate for the pp60v-src tyrosine kinase (see OMIM Ref. No. 190090). Cortactin is overexpressed in carcinoma cells with an amplification of 11q13 and is found in 2 forms, designated p80 and p85. Van Damme et al. (1997) found that in carcinoma cells with the 11q13

amplification, p85 was produced from p80 by posttranslational modification. Also, treatment of these cells with epidermal growth factor (OMIM Ref. No. 131530) or vanadate caused conversion of p80 to p85 and enhanced phosphorylation of the p85 form. Both overexpression and posttranslational modification of cortactin coincided with its redistribution from the cytoplasm to cell-matrix contact sites, implying a role for cortactin in the modulation of cellular adhesive properties.

[22626] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22627] Schuuring, E.; Verhoeven, E.; Mooi, W. J.; Michalides, R. J. A. M. : Identification and cloning of two overexpressed genes, U21B31/PRAD1 and EMS1, within the amplified chromosome 11q13 region in human carcinomas. *Oncogene* 7: 355–361, 1992. ; and

[22628] van Damme, H.; Brok, H.; Schuuring-Scholtes, E.; Schuuring, E. : The redistribution of cortactin into cell-matrix contact sites in human carcinoma cells with 11q13 amplification is asso.

[22629] Further studies establishing the function and utilities of EMS1 are found in John Hopkins OMIM database record ID

164765, and in cited publications numbered 5098–5099 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FXYD Domain Containing Ion Transport Regulator 6 (FXYD6, Accession NM\_022003) is another VGAM497 host target gene. FXYD6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FXYD6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FXYD6 BINDING SITE, designated SEQ ID:22554, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22630] Another function of VGAM497 is therefore inhibition of FXYD Domain Containing Ion Transport Regulator 6 (FXYD6, Accession NM\_022003). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FXYD6. Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 3 (p55, gamma) (PIK3R3, Accession XM\_027982) is another VGAM497 host target gene. PIK3R3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by PIK3R3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIK3R3 BINDING SITE, designated SEQ ID:30609, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22631] Another function of VGAM497 is therefore inhibition of Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 3 (p55, gamma) (PIK3R3, Accession XM\_027982). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIK3R3. Protein Phosphatase 3 (formerly 2B), Catalytic Subunit, Alpha Isoform (calcineurin A alpha) (PPP3CA, Accession NM\_000944) is another VGAM497 host target gene. PPP3CA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP3CA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP3CA BINDING SITE, designated SEQ ID:6648, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3208.

[22632] Another function of VGAM497 is therefore inhibition of Protein Phosphatase 3 (formerly 2B), Catalytic Subunit, Alpha Isoform (calcineurin A alpha) (PPP3CA, Accession NM\_000944), a gene which is the catalytic subunit of calcium-dependent, calmodulin-stimulated protein phosphatase. Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP3CA. The function of PPP3CA has been established by previous studies. Semsarian et al. (1999) and Musaro et al. (1999) independently showed that IGF1 (OMIM Ref. No. 147440) stimulates skeletal muscle hypertrophy and a switch to glycolytic metabolism by activating calcineurin A and inducing the nuclear translocation of transcription factor NFATC1 (OMIM Ref. No. 600489). Semsarian et al. (1999) found that hypertrophy was suppressed by the calcineurin inhibitors cyclosporin A or FK506, but not by inhibitors of the MAP kinase or phosphatidylinositol-3-OH kinase pathways. Musaro et al. (1999) showed that expression of a dominant-negative calcineurin mutant also repressed myocyte differentiation and hypertrophy. Musaro et al. (1999) demonstrated that either IGF1 or activated cal-

calcineurin induces expression of transcription factor GATA2 (OMIM Ref. No. 137295), which accumulates in a subset of myocyte nuclei, where it associates with calcineurin and a specific dephosphorylated isoform of NFATC1. Animal model experiments lend further support to the function of PPP3CA. Winder et al. (1998) generated transgenic mice that overexpressed a truncated form of the murine calcineurin A-alpha catalytic subunit under the control of the CaMKII-alpha promoter. Mice expressing this transgene show increased calcium-dependent phosphatase activity in the hippocampus. Physiologic studies and pharmacologic experiments revealed a novel, intermediate phase of long-term potentiation (I-LTP) in the CA1 region of the hippocampus. This I-LTP differs from the E-LTP (early component of LTP) by requiring multiple trains for induction and in being dependent on PKA (cAMP-dependent protein kinase). It also differs from the L-LTP (late component of LTP) in not requiring new protein synthesis. These data suggested to Winder et al. (1998) that calcineurin acts as an inhibitory constraint on I-LTP that is relieved by PKA, and that this inhibitory constraint acts as a gate to regulate the synaptic induction of L-LTP.

[22633] It is appreciated that the abovementioned animal model

for PPP3CA is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[22634] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22635] Winder, D. G.; Mansuy, I. M.; Osman, M.; Moallem, T. M.; Kandel, E. R. : Genetic and pharmacological evidence for a novel, intermediate phase of long-term potentiation suppressed by calcineurin. Cell 92: 25–37, 1998. ; and

[22636] Fuentes, J. J.; Genesca, L.; Kingsbury, T. J.; Cunningham, K. W.; Perez-Riba, M.; Estivill, X.; de la Luna, S. : DSCR1, overexpressed in Down syndrome, is an inhibitor of calcineurin-me.

[22637] Further studies establishing the function and utilities of PPP3CA are found in John Hopkins OMIM database record ID 114105, and in cited publications numbered 4679–4685, 11673–468 and 11674–4689 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_002838) is another VGAM497 host target gene. PTPRC BINDING SITE1 and PTPRC BINDING SITE2 are HOST TARGET binding sites

found in untranslated regions of mRNA encoded by PTPRC, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPRC BINDING SITE1 and PTPRC BINDING SITE2, designated SEQ ID:8720 and SEQ ID:28146 respectively, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22638] Another function of VGAM497 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_002838). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRC. Syndecan 2 (heparan sulfate proteoglycan 1, cell surface-associated, fibroglycan) (SDC2, Accession XM\_040582) is another VGAM497 host target gene. SDC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDC2 BINDING SITE, designated SEQ ID:33328, to the nucleotide sequence of



VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22639] Another function of VGAM497 is therefore inhibition of Syndecan 2 (heparan sulfate proteoglycan 1, cell surface-associated, fibroglycan) (SDC2, Accession XM\_040582). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDC2. Translocase of Inner Mitochondrial Membrane 8 Homolog A (yeast) (TIMM8A, Accession NM\_004085) is another VGAM497 host target gene. TIMM8A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIMM8A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMM8A BINDING SITE, designated SEQ ID:10288, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22640] Another function of VGAM497 is therefore inhibition of Translocase of Inner Mitochondrial Membrane 8 Homolog A (yeast) (TIMM8A, Accession NM\_004085). Accordingly, utilities of VGAM497 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with TIMM8A. Ubiquitously Transcribed Tetratricopeptide Repeat Gene, Y Chromosome (UTY, Accession NM\_007125) is another VGAM497 host target gene. UTY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UTY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UTY BINDING SITE, designated SEQ ID:13983, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22641] Another function of VGAM497 is therefore inhibition of Ubiquitously Transcribed Tetratricopeptide Repeat Gene, Y Chromosome (UTY, Accession NM\_007125), a gene which is an ubiquitous tetratricopeptide repeat protein with unknown function. Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UTY. The function of UTY has been established by previous studies. Greenfield et al. (1996) described a mouse Y-linked gene, Uty, which is widely expressed and encodes a tetratricopeptide repeat (TPR) protein. TPR motifs are found in a variety of func-

tionally distinct proteins and are believed to mediate protein–protein interaction. The 5.5–kb Uty transcript encodes a 1,186 amino acid protein with 8 TPR motifs in its N terminus. Greenfield et al. (1998) reported that the human UTY gene maps to band 5C. This band is known to contain one or more genes functioning in spermatogenesis and a Y–specific growth gene. See 300128 for a description of the X–linked homolog of UTY. Foresta et al. (2000) reported a complete sequence map of the AZFa region (see OMIM Ref. No. 415000), the genomic structure of AZFa genes, and their deletion analysis in 173 infertile men with well–defined spermatogenic alterations. Deletions were found in 9 patients: DBY (OMIM Ref. No. 400010) alone was deleted in 6, DFFRY (USP9Y; 400005) only in 1, and 1 each with USP9Y–DBY or DBY–UTY missing. No patients solely lacked UTY. Patients lacking DBY exhibited either Sertoli cell–only syndrome or severe hypospermatogenesis. The authors suggested that DBY and USP9Y play key roles in the spermatogenic process.

[22642] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22643] Greenfield, A.; Scott, D.; Pennisi, D.; Ehrmann, I.; Ellis, P.;

Cooper, L.; Simpson, E.; Koopman, P. : An H-YDb epitope is encoded by a novel mouse Y chromosome gene. *Nature Genet.* 14: 474–478, 1996. ; and

[22644] Foresta, C.; Ferlin, A.; Moro, E. : Deletion and expression analysis of AZFa genes on the human Y chromosome revealed a major role for DBY in male infertility. *Hum. Molec. Genet.* 9: 1161–11.

[22645] Further studies establishing the function and utilities of UTY are found in John Hopkins OMIM database record ID 400009, and in cited publications numbered 882 and 10988 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. AOP2 (Accession NM\_004905) is another VGAM497 host target gene. AOP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AOP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AOP2 BINDING SITE, designated SEQ ID:11342, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22646] Another function of VGAM497 is therefore inhibition of AOP2 (Accession NM\_004905). Accordingly, utilities of

VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AOP2.

AUT-like 1, Cysteine Endopeptidase (*S. cerevisiae*) (AUTL1, Accession NM\_032852) is another VGAM497 host target gene. AUTL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AUTL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AUTL1 BINDING SITE, designated SEQ ID:26651, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22647] Another function of VGAM497 is therefore inhibition of AUT-like 1, Cysteine Endopeptidase (*S. cerevisiae*) (AUTL1, Accession NM\_032852). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AUTL1. FLJ10719 (Accession XM\_031328) is another VGAM497 host target gene. FLJ10719 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10719, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10719 BINDING SITE, designated SEQ ID:31341, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22648] Another function of VGAM497 is therefore inhibition of FLJ10719 (Accession XM\_031328). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10719. FLJ12586 (Accession NM\_024620) is another VGAM497 host target gene. FLJ12586 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12586, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12586 BINDING SITE, designated SEQ ID:23884, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22649] Another function of VGAM497 is therefore inhibition of FLJ12586 (Accession NM\_024620). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12586.

KIAA1309 (Accession NM\_033495) is another VGAM497 host target gene. KIAA1309 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1309, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1309 BINDING SITE, designated SEQ ID:27265, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22650] Another function of VGAM497 is therefore inhibition of KIAA1309 (Accession NM\_033495). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1309. MDN1, Midasin Homolog (yeast) (MDN1, Accession XM\_031539) is another VGAM497 host target gene. MDN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MDN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MDN1 BINDING SITE, designated SEQ ID:31411, to the nucleotide sequence of VGAM497 RNA,

herein designated VGAM RNA, also designated SEQ ID:3208.

[22651] Another function of VGAM497 is therefore inhibition of MDN1, Midasin Homolog (yeast) (MDN1, Accession XM\_031539). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MDN1. MGC16385 (Accession NM\_145039) is another VGAM497 host target gene. MGC16385 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC16385, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC16385 BINDING SITE, designated SEQ ID:29663, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22652] Another function of VGAM497 is therefore inhibition of MGC16385 (Accession NM\_145039). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC16385. NET-6 (Accession NM\_014399) is another VGAM497 host target gene. NET-6 BINDING SITE is HOST



TARGET binding site found in the 3` untranslated region of mRNA encoded by NET-6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NET-6 BINDING SITE, designated SEQ ID:15741, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22653] Another function of VGAM497 is therefore inhibition of NET-6 (Accession NM\_014399). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NET-6. PRO0246 (Accession NM\_014123) is another VGAM497 host target gene. PRO0246 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO0246, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0246 BINDING SITE, designated SEQ ID:15382, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22654] Another function of VGAM497 is therefore inhibition of

PRO0246 (Accession NM\_014123). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0246. Synaptophysin-like Protein (SYPL, Accession XM\_167511) is another VGAM497 host target gene. SYPL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SYPL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYPL BINDING SITE, designated SEQ ID:44647, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22655] Another function of VGAM497 is therefore inhibition of Synaptophysin-like Protein (SYPL, Accession XM\_167511). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYPL. VEZATIN (Accession NM\_017599) is another VGAM497 host target gene. VEZATIN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VEZATIN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of VEZATIN BINDING SITE, designated SEQ ID:19072, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22656] Another function of VGAM497 is therefore inhibition of VEZATIN (Accession NM\_017599). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VEZATIN. LOC122525 (Accession XM\_071793) is another VGAM497 host target gene. LOC122525 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC122525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC122525 BINDING SITE, designated SEQ ID:37421, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22657] Another function of VGAM497 is therefore inhibition of LOC122525 (Accession XM\_071793). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC122525. LOC147495 (Accession XM\_097240) is an-

other VGAM497 host target gene. LOC147495 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147495, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147495 BINDING SITE, designated SEQ ID:40840, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22658] Another function of VGAM497 is therefore inhibition of LOC147495 (Accession XM\_097240). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147495. LOC148254 (Accession XM\_086121) is another VGAM497 host target gene. LOC148254 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148254, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148254 BINDING SITE, designated SEQ ID:38506, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22659] Another function of VGAM497 is therefore inhibition of LOC148254 (Accession XM\_086121). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148254. LOC196411 (Accession XM\_113714) is another VGAM497 host target gene. LOC196411 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196411, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196411 BINDING SITE, designated SEQ ID:42367, to the nucleotide sequence of VGAM497 RNA, herein designated VGAM RNA, also designated SEQ ID:3208.

[22660] Another function of VGAM497 is therefore inhibition of LOC196411 (Accession XM\_113714). Accordingly, utilities of VGAM497 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196411. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 498 (VGAM498) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[22661] VGAM498 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM498 was detected is described hereinabove with reference to Figs. 1–8.

[22662] VGAM498 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 7. VGAM498 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22663] VGAM498 gene encodes a VGAM498 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM498 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM498 precursor RNA is designated SEQ ID:484, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:484 is located at position 127367 relative to the genome of Human Herpesvirus 7.

[22664] VGAM498 precursor RNA folds onto itself, forming VGAM498 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[22665] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM498 folded precursor RNA into VGAM498 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 77%) nucleotide se-  
quence of VGAM498 RNA is designated SEQ ID:3209, and  
is provided hereinbelow with reference to the sequence  
listing part.

[22666] VGAM498 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM498 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM498 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22667] VGAM498 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM498 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM498 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM498 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM498 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in



the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22668] The complementary binding of VGAM498 RNA, herein designated VGAM RNA, to host target binding sites on VGAM498 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM498 host target RNA into VGAM498 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22669] It is appreciated that VGAM498 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM498 host target genes. The mRNA of each one of this plurality of VGAM498 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM498 RNA, herein designated VGAM RNA, and which when bound by VGAM498 RNA causes inhibition of translation of respective one or more VGAM498 host target proteins.

[22670] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM498 gene, herein designated VGAM GENE, on one or more VGAM498 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22671] It is yet further appreciated that a function of VGAM498 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 7. Specific functions, and accordingly utilities, of VGAM498 correlate with, and may be deduced from, the identity of the host target genes which VGAM498 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

[22672] Nucleotide sequences of the VGAM498 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM498 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM498 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM498 are further described hereinbelow with reference to Table 1.

[22673] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM498 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM498 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22674] As mentioned hereinabove with reference to Fig. 1, a function of VGAM498 gene, herein designated VGAM is inhibition of expression of VGAM498 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM498 correlate with, and may be deduced from, the identity of the target genes which VGAM498 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22675] Ankyrin 1, Erythrocytic (ANK1, Accession XM\_016774) is a VGAM498 host target gene. ANK1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ANK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANK1 BINDING SITE, designated SEQ ID:30289, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22676] A function of VGAM498 is therefore inhibition of Ankyrin 1, Erythrocytic (ANK1, Accession XM\_016774). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANK1. Contactin 3 (plasmacytoma associated) (CNTN3, Accession XM\_039627) is another VGAM498 host target gene. CNTN3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CNTN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNTN3 BINDING SITE, designated SEQ ID:33133, to the nucleotide sequence of VGAM498

RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22677] Another function of VGAM498 is therefore inhibition of Contactin 3 (plasmacytoma associated) (CNTN3, Accession XM\_039627), a gene which may play a role in the initial growth and guidance of axons. Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNTN3. The function of CNTN3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM420. Collagen, Type I, Alpha 1 (COL1A1, Accession NM\_000088) is another VGAM498 host target gene. COL1A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COL1A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COL1A1 BINDING SITE, designated SEQ ID:5539, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22678] Another function of VGAM498 is therefore inhibition of

Collagen, Type I, Alpha 1 (COL1A1, Accession NM\_000088). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COL1A1. Hyaluronan Synthase 3 (HAS3, Accession NM\_005329) is another VGAM498 host target gene. HAS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HAS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HAS3 BINDING SITE, designated SEQ ID:11803, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22679] Another function of VGAM498 is therefore inhibition of Hyaluronan Synthase 3 (HAS3, Accession NM\_005329), a gene which plays a role in hyaluronan/hyaluronic acid (ha) synthesis. Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HAS3. The function of HAS3 has been established by previous studies. Hyaluronan (HA) is an unbranched glycosaminoglycan composed of repeating disaccharide units. It is a major constituent of the ex-

tracellular matrix and has been implicated in development, tumorigenesis, and several diseases. HA is synthesized at the inner face of the plasma membrane and is subsequently extruded to the outside of the cell. By degenerate PCR, Spicer et al. (1997) isolated a genomic fragment of human HA synthase-3 (HAS3) and genomic and cDNA clones of mouse Has3. The amino acid sequences encoded by the partial HAS3 fragment and the corresponding region of Has3 are 99% conserved. The authors noted that the high degree of sequence conservation between specific human and mouse HASs contrasts with the lower level of identity between HASs within a species, suggesting an evolutionary conservation of functionally important residues and differences in the mode of action of the various HASs. The predicted 554-amino acid Has3 has several consensus HA-binding motifs and multiple transmembrane domains, with 2 at the N terminus and a cluster at the C terminus. Expression of Has3 in COS-1 cells led to high levels of HA biosynthesis. Northern blot analysis of the mouse embryo showed that Has3 is predominantly expressed at late gestation as a major, approximately 6.0- to 6.5-kb transcript and a minor, approximately 4.0-kb transcript. By PCR screening somatic

cell hybrid DNAs and a YAC contig, Spicer et al. (1997) localized the human HAS3 gene to 16q22.1. By interspecific backcross analysis, they mapped the mouse Has3 gene to chromosome 8. Since HAS1 (OMIM Ref. No. 601463), HAS2 (OMIM Ref. No. 601636), and HAS3 are located on different autosomes, Spicer et al. (1997) suggested that the HAS gene family arose comparatively early in vertebrate evolution by sequential duplication of an ancestral HAS gene.

[22680] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22681] Spicer, A. P.; Olson, J. S.; McDonald, J. A. : Molecular cloning and characterization of a cDNA encoding the third putative mammalian hyaluronan synthase. J. Biol. Chem. 272: 8957–8961, 1997. ; and

[22682] Spicer, A. P.; Seldin, M. F.; Olsen, A. S.; Brown, N.; Wells, D. E.; Doggett, N. A.; Itano, N.; Kimata, K.; Inazawa, J.; McDonald, J. A. : Chromosomal localization of the human and mous.

[22683] Further studies establishing the function and utilities of HAS3 are found in John Hopkins OMIM database record ID 602428, and in cited publications numbered 8915 listed



in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Phosphatase 1, Regulatory (inhibitor) Subunit 12B (PPP1R12B, Accession NM\_032104) is another VGAM498 host target gene.

PPP1R12B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1R12B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R12B BINDING SITE, designated SEQ ID:25797, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22684] Another function of VGAM498 is therefore inhibition of Protein Phosphatase 1, Regulatory (inhibitor) Subunit 12B (PPP1R12B, Accession NM\_032104). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R12B. Protein Tyrosine Phosphatase Type IVA, Member 2 (PTP4A2, Accession NM\_080392) is another VGAM498 host target gene. PTP4A2 BINDING SITE1 and PTP4A2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by

PTP4A2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTP4A2 BINDING SITE1 and PTP4A2 BINDING SITE2, designated SEQ ID:27832 and SEQ ID:9555 respectively, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22685] Another function of VGAM498 is therefore inhibition of Protein Tyrosine Phosphatase Type IVA, Member 2 (PTP4A2, Accession NM\_080392), a gene which is a protein tyrosine phosphatase which has a C-terminal prenylation site. Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTP4A2. The function of PTP4A2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM217. Usher Syndrome 3A (USH3A, Accession NM\_052995) is another VGAM498 host target gene. USH3A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by USH3A, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USH3A BINDING SITE, designated SEQ ID:27565, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22686] Another function of VGAM498 is therefore inhibition of Usher Syndrome 3A (USH3A, Accession NM\_052995). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USH3A. Vitamin D (1,25– dihydroxyvitamin D3) Receptor (VDR, Accession NM\_000376) is another VGAM498 host target gene. VDR BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by VDR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VDR BINDING SITE, designated SEQ ID:5944, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22687] Another function of VGAM498 is therefore inhibition of Vitamin D (1,25– dihydroxyvitamin D3) Receptor (VDR,

Accession NM\_000376). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VDR. 20D7-FC4 (Accession XM\_027578) is another VGAM498 host target gene. 20D7-FC4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by 20D7-FC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of 20D7-FC4 BINDING SITE, designated SEQ ID:30537, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22688] Another function of VGAM498 is therefore inhibition of 20D7-FC4 (Accession XM\_027578). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with 20D7-FC4. Cbp/p300-interacting Transactivator, with Glu/Asp-rich Carboxy-terminal Domain, 2 (CITED2, Accession NM\_006079) is another VGAM498 host target gene. CITED2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CITED2, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CITED2 BINDING SITE, designated SEQ ID:12725, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22689] Another function of VGAM498 is therefore inhibition of Cbp/p300–interacting Transactivator, with Glu/Asp–rich Carboxy–terminal Domain, 2 (CITED2, Accession NM\_006079). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CITED2. DKFZP434L187 (Accession XM\_044070) is another VGAM498 host target gene. DKFZP434L187 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZP434L187, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434L187 BINDING SITE, designated SEQ ID:34124, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22690] Another function of VGAM498 is therefore inhibition of

DKFZP434L187 (Accession XM\_044070). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434L187. FLJ13868 (Accession NM\_022744) is another VGAM498 host target gene. FLJ13868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13868 BINDING SITE, designated SEQ ID:22955, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22691] Another function of VGAM498 is therefore inhibition of FLJ13868 (Accession NM\_022744). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13868. FLJ20070 (Accession NM\_017652) is another VGAM498 host target gene. FLJ20070 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20070, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ20070 BINDING SITE, designated SEQ ID:19161, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22692] Another function of VGAM498 is therefore inhibition of FLJ20070 (Accession NM\_017652). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20070. FLJ20154 (Accession XM\_053688) is another VGAM498 host target gene. FLJ20154 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20154, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20154 BINDING SITE, designated SEQ ID:36104, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22693] Another function of VGAM498 is therefore inhibition of FLJ20154 (Accession XM\_053688). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20154. HSNOV1 (Accession NM\_017515) is another VGAM498

host target gene. HSNOV1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSNOV1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSNOV1 BINDING SITE, designated SEQ ID:18967, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22694] Another function of VGAM498 is therefore inhibition of HSNOV1 (Accession NM\_017515). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSNOV1. KIAA0237 (Accession NM\_014747) is another VGAM498 host target gene. KIAA0237 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0237 BINDING SITE, designated SEQ ID:16440, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.



[22695] Another function of VGAM498 is therefore inhibition of KIAA0237 (Accession NM\_014747). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0237. KIAA0286 (Accession XM\_043118) is another VGAM498 host target gene. KIAA0286 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0286, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0286 BINDING SITE, designated SEQ ID:33903, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22696] Another function of VGAM498 is therefore inhibition of KIAA0286 (Accession XM\_043118). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0286. PDZ-GEF1 (Accession NM\_014247) is another VGAM498 host target gene. PDZ-GEF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDZ-GEF1, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDZ-GEF1 BINDING SITE, designated SEQ ID:15521, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22697] Another function of VGAM498 is therefore inhibition of PDZ-GEF1 (Accession NM\_014247). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDZ-GEF1. LOC151610 (Accession XM\_087245) is another VGAM498 host target gene. LOC151610 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151610, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151610 BINDING SITE, designated SEQ ID:39138, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22698] Another function of VGAM498 is therefore inhibition of LOC151610 (Accession XM\_087245). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC151610. LOC163231 (Accession XM\_092094) is another VGAM498 host target gene. LOC163231 BINDING SITE1 and LOC163231 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC163231, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163231 BINDING SITE1 and LOC163231 BINDING SITE2, designated SEQ ID:40100 and SEQ ID:40101 respectively, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22699] Another function of VGAM498 is therefore inhibition of LOC163231 (Accession XM\_092094). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163231. LOC254973 (Accession XM\_172751) is another VGAM498 host target gene. LOC254973 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254973, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC254973 BINDING SITE, designated SEQ ID:46077, to the nucleotide sequence of VGAM498 RNA, herein designated VGAM RNA, also designated SEQ ID:3209.

[22700] Another function of VGAM498 is therefore inhibition of LOC254973 (Accession XM\_172751). Accordingly, utilities of VGAM498 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254973. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 499 (VGAM499) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22701] VGAM499 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM499 was detected is described hereinabove with reference to Figs. 1–8.

[22702] VGAM499 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Strawberry Vein Banding Virus (SVBV). VGAM499 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22703] VGAM499 gene encodes a VGAM499 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM499 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM499 precursor RNA is designated SEQ ID:485, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:485 is located at position 4662 relative to the genome of Strawberry Vein Banding Virus (SVBV).

[22704] VGAM499 precursor RNA folds onto itself, forming VGAM499 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22705] An enzyme complex designated DICER COMPLEX, `dices` the VGAM499 folded precursor RNA into VGAM499 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 58%) nucleotide sequence of VGAM499 RNA is designated SEQ ID:3210, and is provided hereinbelow with reference to the sequence listing part.

[22706] VGAM499 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM499 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM499 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22707] VGAM499 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM499 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM499 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM499 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM499 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22708] The complementary binding of VGAM499 RNA, herein designated VGAM RNA, to host target binding sites on VGAM499 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM499 host target RNA into VGAM499 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22709] It is appreciated that VGAM499 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM499 host target genes. The mRNA of each one of this plurality of VGAM499 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM499 RNA, herein designated VGAM RNA, and which when bound by VGAM499 RNA causes inhibition of translation of respective one or more VGAM499 host target proteins.

[22710] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM499 gene, herein designated VGAM GENE, on one or more VGAM499 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these



other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[22711] It is yet further appreciated that a function of VGAM499 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of viral infection by Strawberry Vein Banding Virus (SVBV). Specific functions, and accordingly utilities, of VGAM499 correlate with, and may be deduced from, the identity of the host target genes which VGAM499 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22712] Nucleotide sequences of the VGAM499 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM499 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM499 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM499 are further described hereinbelow with reference to Table 1.

[22713] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM499 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM499 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22714] As mentioned hereinabove with reference to Fig. 1, a function of VGAM499 gene, herein designated VGAM is inhibition of expression of VGAM499 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM499 correlate with, and may be deduced from, the identity of the target genes which VGAM499 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22715] Pallidin Homolog (mouse) (PLDN, Accession NM\_012388) is a VGAM499 host target gene. PLDN BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PLDN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLDN BINDING SITE, designated SEQ ID:14743, to the nucleotide sequence of VGAM499 RNA, herein designated VGAM RNA, also designated SEQ ID:3210.

[22716] A function of VGAM499 is therefore inhibition of Pallidin

Homolog (mouse) (PLDN, Accession NM\_012388), a gene which may play a role in intracellular vesicle trafficking. Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLDN. The function of PLDN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM138.DKFZp547A023 (Accession XM\_052065) is another VGAM499 host target gene. DKFZp547A023 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547A023, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547A023 BINDING SITE, designated SEQ ID:35942, to the nucleotide sequence of VGAM499 RNA, herein designated VGAM RNA, also designated SEQ ID:3210.

[22717] Another function of VGAM499 is therefore inhibition of DKFZp547A023 (Accession XM\_052065). Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547A023. FLJ13902 (Accession NM\_024653) is

another VGAM499 host target gene. FLJ13902 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13902, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13902 BINDING SITE, designated SEQ ID:23950, to the nucleotide sequence of VGAM499 RNA, herein designated VGAM RNA, also designated SEQ ID:3210.

[22718] Another function of VGAM499 is therefore inhibition of FLJ13902 (Accession NM\_024653). Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13902. KIAA0429 (Accession NM\_014751) is another VGAM499 host target gene. KIAA0429 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0429, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0429 BINDING SITE, designated SEQ ID:16464, to the nucleotide sequence of VGAM499 RNA, herein designated VGAM RNA, also designated SEQ ID:3210.

[22719] Another function of VGAM499 is therefore inhibition of KIAA0429 (Accession NM\_014751). Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0429. KIAA0446 (Accession XM\_044155) is another VGAM499 host target gene. KIAA0446 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0446 BINDING SITE, designated SEQ ID:34151, to the nucleotide sequence of VGAM499 RNA, herein designated VGAM RNA, also designated SEQ ID:3210.

[22720] Another function of VGAM499 is therefore inhibition of KIAA0446 (Accession XM\_044155). Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0446. LOC143888 (Accession XM\_084669) is another VGAM499 host target gene. LOC143888 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143888, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143888 BINDING SITE, designated SEQ ID:37665, to the nucleotide sequence of VGAM499 RNA, herein designated VGAM RNA, also designated SEQ ID:3210.

[22721] Another function of VGAM499 is therefore inhibition of LOC143888 (Accession XM\_084669). Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143888. LOC254266 (Accession XM\_173221) is another VGAM499 host target gene. LOC254266 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254266, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254266 BINDING SITE, designated SEQ ID:46480, to the nucleotide sequence of VGAM499 RNA, herein designated VGAM RNA, also designated SEQ ID:3210.

[22722] Another function of VGAM499 is therefore inhibition of LOC254266 (Accession XM\_173221). Accordingly, utilities of VGAM499 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC254266. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 500 (VGAM500) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22723] VGAM500 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM500 was detected is described hereinabove with reference to Figs. 1–8.

[22724] VGAM500 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Strawberry Vein Banding Virus (SVBV). VGAM500 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22725] VGAM500 gene encodes a VGAM500 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM500 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM500 precursor RNA is designated SEQ ID:486, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:486 is located at position 4531 relative to the genome of Strawberry Vein Banding Virus (SVBV).

[22726] VGAM500 precursor RNA folds onto itself, forming VGAM500 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22727] An enzyme complex designated DICER COMPLEX, `dices` the VGAM500 folded precursor RNA into VGAM500 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM500 RNA is designated SEQ ID:3211, and is provided hereinbelow with reference to the sequence listing part.



[22728] VGAM500 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM500 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM500 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22729] VGAM500 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM500 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM500 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM500 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM500 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22730] The complementary binding of VGAM500 RNA, herein designated VGAM RNA, to host target binding sites on VGAM500 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM500 host target RNA into VGAM500 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22731] It is appreciated that VGAM500 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM500 host target genes. The mRNA of each one of this plurality of VGAM500 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM500 RNA, herein designated VGAM RNA, and which when bound by VGAM500 RNA causes in-

hibition of translation of respective one or more VGAM500 host target proteins.

[22732] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM500 gene, herein designated VGAM GENE, on one or more VGAM500 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22733] It is yet further appreciated that a function of VGAM500 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM500 include diagnosis, prevention and

treatment of viral infection by Strawberry Vein Banding Virus (SVBV). Specific functions, and accordingly utilities, of VGAM500 correlate with, and may be deduced from, the identity of the host target genes which VGAM500 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22734] Nucleotide sequences of the VGAM500 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM500 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM500 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM500 are further described hereinbelow with reference to Table 1.

[22735] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM500 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM500 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22736] As mentioned hereinabove with reference to Fig. 1, a function of VGAM500 gene, herein designated VGAM is inhibition of expression of VGAM500 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM500 correlate with, and may be deduced from, the identity of the target genes which VGAM500 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22737] Adaptor-related Protein Complex 1, Mu 1 Subunit (AP1M1, Accession NM\_032493) is a VGAM500 host target gene. AP1M1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AP1M1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP1M1 BINDING SITE, designated SEQ ID:26244, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22738] A function of VGAM500 is therefore inhibition of Adaptor-related Protein Complex 1, Mu 1 Subunit (AP1M1, Accession NM\_032493), a gene which promotes the formation of clathrin-coated pits and vesicles. Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP1M1. The function of AP1M1 has been established by previous

studies. Heterotetrameric adaptor complexes promote the formation of clathrin-coated pits and vesicles. The AP-1 adaptor, localized at the trans-Golgi network, is composed of 2 approximately 100-kD subunits, beta-prime adaptin (OMIM Ref. No. 600157) and gamma-adaptin (OMIM Ref. No. 603533); a medium subunit, AP47; and a small subunit, AP19 (OMIM Ref. No. 603531). Nakayama et al. (1991) isolated a mouse brain cDNA encoding AP47.

[22739] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22740] Doray, B.; Ghosh, P.; Griffith, J.; Geuze, H. J.; Kornfeld, S. : Cooperation of GGAs and AP-1 in packaging MPRs at the trans-Golgi network. Science 297: 1700-1703, 2002. ; and

[22741] Nakayama, Y.; Goebel, M.; O'Brine Greco, B.; Lemmon, S.; Pingchang Chow, E.; Kirchhausen, T. : The medium chains of the mammalian clathrin-associated proteins have a homolog in yeast. E.

[22742] Further studies establishing the function and utilities of AP1M1 are found in John Hopkins OMIM database record ID 603535, and in cited publications numbered 12596, 422 and 8521 listed in the bibliography section hereinbe-

low, which are also hereby incorporated by reference. ARPP-21 (Accession NM\_016300) is another VGAM500 host target gene. ARPP-21 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ARPP-21, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARPP-21 BINDING SITE, designated SEQ ID:18420, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22743] Another function of VGAM500 is therefore inhibition of ARPP-21 (Accession NM\_016300). Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARPP-21. JM4 (Accession NM\_007213) is another VGAM500 host target gene. JM4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JM4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JM4 BINDING SITE, designated SEQ ID:14079, to the nucleotide sequence of VGAM500 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3211.

[22744] Another function of VGAM500 is therefore inhibition of JM4 (Accession NM\_007213). Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JM4. MGC4309 (Accession NM\_024115) is another VGAM500 host target gene. MGC4309 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4309, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4309 BINDING SITE, designated SEQ ID:23569, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22745] Another function of VGAM500 is therefore inhibition of MGC4309 (Accession NM\_024115). Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4309. TED (Accession NM\_015686) is another VGAM500 host target gene. TED BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TED, corresponding to a HOST TAR-



GET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TED BINDING SITE, designated SEQ ID:17917, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22746] Another function of VGAM500 is therefore inhibition of TED (Accession NM\_015686). Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TED. Zinc Finger Protein 273 (ZNF273, Accession XM\_088082) is another VGAM500 host target gene. ZNF273 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZNF273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF273 BINDING SITE, designated SEQ ID:39509, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22747] Another function of VGAM500 is therefore inhibition of Zinc Finger Protein 273 (ZNF273, Accession XM\_088082). Accordingly, utilities of VGAM500 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with ZNF273. LOC145934 (Accession XM\_096905) is another VGAM500 host target gene. LOC145934 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145934, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145934 BINDING SITE, designated SEQ ID:40626, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22748] Another function of VGAM500 is therefore inhibition of LOC145934 (Accession XM\_096905). Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145934. LOC256444 (Accession XM\_172937) is another VGAM500 host target gene. LOC256444 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC256444, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC256444 BINDING SITE, designated SEQ ID:46199, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22749] Another function of VGAM500 is therefore inhibition of LOC256444 (Accession XM\_172937). Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256444. LOC257484 (Accession XM\_114232) is another VGAM500 host target gene. LOC257484 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257484, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257484 BINDING SITE, designated SEQ ID:42815, to the nucleotide sequence of VGAM500 RNA, herein designated VGAM RNA, also designated SEQ ID:3211.

[22750] Another function of VGAM500 is therefore inhibition of LOC257484 (Accession XM\_114232). Accordingly, utilities of VGAM500 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257484. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 501 (VGAM501) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22751] VGAM501 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM501 was detected is described hereinabove with reference to Figs. 1–8.

[22752] VGAM501 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Carrot Mottle Mimic Virus. VGAM501 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22753] VGAM501 gene encodes a VGAM501 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM501 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM501 precursor RNA is designated SEQ ID:487, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:487 is located at position 2430 relative to the genome of Carrot

## Mottle Mimic Virus.

[22754] VGAM501 precursor RNA folds onto itself, forming VGAM501 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22755] An enzyme complex designated DICER COMPLEX, `dices` the VGAM501 folded precursor RNA into VGAM501 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM501 RNA is designated SEQ ID:3212, and is provided hereinbelow with reference to the sequence listing part.

[22756] VGAM501 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM501 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM501 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[22757] VGAM501 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM501 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM501 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM501 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM501 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22758] The complementary binding of VGAM501 RNA, herein designated VGAM RNA, to host target binding sites on VGAM501 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM501 host target RNA into VGAM501 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22759] It is appreciated that VGAM501 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM501 host target genes. The mRNA of each one of this plurality of VGAM501 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM501 RNA, herein designated VGAM RNA, and which when bound by VGAM501 RNA causes inhibition of translation of respective one or more VGAM501 host target proteins.

[22760] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM501 gene, herein designated VGAM GENE, on one or more VGAM501 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22761] It is yet further appreciated that a function of VGAM501 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM501 include diagnosis, prevention and treatment of viral infection by Carrot Mottle Mimic Virus. Specific functions, and accordingly utilities, of VGAM501



correlate with, and may be deduced from, the identity of the host target genes which VGAM501 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22762] Nucleotide sequences of the VGAM501 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM501 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM501 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM501 are further described hereinbelow with reference to Table 1.

[22763] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM501 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM501 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22764] As mentioned hereinabove with reference to Fig. 1, a function of VGAM501 gene, herein designated VGAM is inhibition of expression of VGAM501 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM501 correlate with, and may be deduced

from, the identity of the target genes which VGAM501 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22765] Eukaryotic Translation Initiation Factor 4E Binding Protein 2 (EIF4EBP2, Accession NM\_004096) is a VGAM501 host target gene. EIF4EBP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF4EBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF4EBP2 BINDING SITE, designated SEQ ID:10301, to the nucleotide sequence of VGAM501 RNA, herein designated VGAM RNA, also designated SEQ ID:3212.

[22766] A function of VGAM501 is therefore inhibition of Eukaryotic Translation Initiation Factor 4E Binding Protein 2 (EIF4EBP2, Accession NM\_004096), a gene which binds EIF4E and negatively regulates initiation of translation. Accordingly, utilities of VGAM501 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF4EBP2. The function of EIF4EBP2 has been established by previous studies. Pause et al. (1994) reported that the 4EBP2 gene encodes a 120-amino acid

polypeptide that is 56% identical to that of 4EBP1 (OMIM Ref. No. 602223). By Northern blot analysis, Tsukiyama-Kohara et al. (1996) showed that a major 3.5-kb transcript of 4EBP2 is expressed ubiquitously. Tsukiyama-Kohara et al. (1996) analyzed the genomic structure of the mouse EIF4EBP2 gene and showed that it consists of 3 exons and spans 20 kb. Its intron/exon structure is identical to that of EIF4EBP1. Using fluorescence in situ hybridization, Tsukiyama-Kohara et al. (1996) mapped the EIF4EBP2 gene to human chromosome 10q21-q22. They noted that chromosomal alterations in this region have been found in some human cancers. Tsukiyama-Kohara et al. (1996) mapped the mouse 4EBP2 gene to chromosome 10B4-B5.

[22767] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22768] Pause, A.; Belsham, G. J.; Gingras, A.-C.; Donze, O.; Lin, T.-A.; Lawrence, J. C., Jr.; Sonenberg, N. : Insulin-dependent stimulation of protein synthesis by phosphorylation of a regulator of 5-prime-cap function. *Nature* 371: 762-767, 1994. ; and

[22769] Tsukiyama-Kohara, K.; Vidal, S. M.; Gingras, A.-C.; Glover, T. W.; Hanash, S. M.; Heng, H.; Sonenberg, N. : Tissue dis-

tribution, genomic structure, and chromosome mapping of mouse and h.

[22770] Further studies establishing the function and utilities of EIF4EBP2 are found in John Hopkins OMIM database record ID 602224, and in cited publications numbered 346 and 6286 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Suppressor of Variegation 3-9 Homolog 1 (Drosophila) (SUV39H1, Accession NM\_003173) is another VGAM501 host target gene. SUV39H1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SUV39H1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SUV39H1 BINDING SITE, designated SEQ ID:9147, to the nucleotide sequence of VGAM501 RNA, herein designated VGAM RNA, also designated SEQ ID:3212.

[22771] Another function of VGAM501 is therefore inhibition of Suppressor of Variegation 3-9 Homolog 1 (Drosophila) (SUV39H1, Accession NM\_003173), a gene which is homolog of Drosophila suppressor of variegation 3-9 and modifies position effect variegation. Accordingly, utilities

of VGAM501 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SUV39H1. The function of SUV39H1 has been established by previous studies. By screening a human B-cell cDNA library with a sequence encoding the C-terminal portion of the *Drosophila* Su(var)3-9 gene product, which contains the SET domain, Aagaard et al. (1999) isolated a cDNA encoding SUV39H1. The predicted 412-amino acid SUV39H1 protein contains a chromodomain that is located close to the N terminus, a cysteine-rich region, an adjacent C-terminal SET domain that is followed at the very C-terminal tail by 3 conserved cysteine residues, and a putative nuclear localization signal. SUV39H1 shares 95% amino acid sequence identity with mouse Suv39h1, 42% identity with *Drosophila* Su(var)3-9, and 38% identity with *S. pombe* CLR4, another Su(var)3-9 ortholog. Immunoblot analysis of protein extracts from human cell lines detected an approximately 48-kD endogenous SUV39H1 protein, a mass that corresponds with the mass calculated from the SUV39H1 cDNA. Immunodetection of endogenous SUV39H1 protein revealed enriched distribution at heterochromatic foci during interphase and centromere-specific localization during metaphase. In addition, SUV39H1

protein associated with M31 (HP1-beta, or CBX1; 604511), an Su(var) homolog, indicating the existence of an Su(var) protein complex. Animal model experiments lend further support to the function of SUV39H1. Peters et al. (2001) generated mice deficient for either Suv39h1 or Suv39h2 (OMIM Ref. No. 606503). These animals displayed normal viability and fertility and did not exhibit apparent phenotypes. The authors subsequently intercrossed Suv39h1 -/- and Suv39h2 -/- mice to generate compound Suv39h mutants that were then used to derive Suv39h double-null mice (Suv39h1 -/- and Suv39h2 -/-). These mice displayed severely impaired viability and chromosomal instabilities that were associated with an increased tumor risk and perturbed chromosome interactions during male meiosis. These data suggested a crucial role for pericentric H3 histone-lys9 methylation in protecting genome stability and defined the Suv39h HMTases as important epigenetic regulators for mammalian development.

[22772] It is appreciated that the abovementioned animal model for SUV39H1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[22773] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [22774] Aagaard, L.; Laible, G.; Selenko, P.; Schmid, M.; Dorn, R.; Schotta, G.; Kuhfittig, S.; Wolf, A.; Lebersorger, A.; Singh, P. B.; Reuter, G.; Jenuwein, T. : Functional mammalian homologues of the Drosophila PEV-modifier Su(var)3-9 encode centromere-associated proteins which complex with the heterochromatin component M31. EMBO J. 18: 1923-1938, 1999. ; and
- [22775] Peters, A. H. F. M.; O'Carroll, D.; Scherthan, H.; Mechtler, K.; Sauer, S.; Schofer, C.; Weipoltshammer, K.; Pagani, M.; Lachner, M.; Kohlmaier, A.; Opravil, S.; Doyle, M.; Sibilia, M.
- [22776] Further studies establishing the function and utilities of SUV39H1 are found in John Hopkins OMIM database record ID 300254, and in cited publications numbered 1244-124 and 9068-9073 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Claudin 8 (CLDN8, Accession NM\_012132) is another VGAM501 host target gene. CLDN8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLDN8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLDN8 BINDING SITE, designated SEQ ID:14443, to the nucleotide sequence of VGAM501 RNA, herein designated VGAM RNA, also designated SEQ ID:3212.

[22777] Another function of VGAM501 is therefore inhibition of Claudin 8 (CLDN8, Accession NM\_012132). Accordingly, utilities of VGAM501 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLDN8. FLJ11267 (Accession NM\_019607) is another VGAM501 host target gene. FLJ11267 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11267, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11267 BINDING SITE, designated SEQ ID:21223, to the nucleotide sequence of VGAM501 RNA, herein designated VGAM RNA, also designated SEQ ID:3212.

[22778] Another function of VGAM501 is therefore inhibition of FLJ11267 (Accession NM\_019607). Accordingly, utilities of VGAM501 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11267.



KIAA0090 (Accession XM\_114045) is another VGAM501 host target gene. KIAA0090 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0090, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0090 BINDING SITE, designated SEQ ID:42649, to the nucleotide sequence of VGAM501 RNA, herein designated VGAM RNA, also designated SEQ ID:3212.

[22779] Another function of VGAM501 is therefore inhibition of KIAA0090 (Accession XM\_114045). Accordingly, utilities of VGAM501 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0090. LOC221687 (Accession XM\_166423) is another VGAM501 host target gene. LOC221687 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221687 BINDING SITE, designated SEQ ID:44305, to the nucleotide sequence of VGAM501 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3212.

[22780] Another function of VGAM501 is therefore inhibition of LOC221687 (Accession XM\_166423). Accordingly, utilities of VGAM501 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221687. LOC253769 (Accession XM\_173183) is another VGAM501 host target gene. LOC253769 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253769, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253769 BINDING SITE, designated SEQ ID:46429, to the nucleotide sequence of VGAM501 RNA, herein designated VGAM RNA, also designated SEQ ID:3212.

[22781] Another function of VGAM501 is therefore inhibition of LOC253769 (Accession XM\_173183). Accordingly, utilities of VGAM501 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253769. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 502 (VGAM502) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22782] VGAM502 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM502 was detected is described hereinabove with reference to Figs. 1–8.

[22783] VGAM502 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Carrot Mottle Mimic Virus. VGAM502 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22784] VGAM502 gene encodes a VGAM502 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM502 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM502 precursor RNA is designated SEQ ID:488, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:488 is located at position 2271 relative to the genome of Carrot Mottle Mimic Virus.

[22785] VGAM502 precursor RNA folds onto itself, forming

VGAM502 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22786] An enzyme complex designated DICER COMPLEX, `dices` the VGAM502 folded precursor RNA into VGAM502 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM502 RNA is designated SEQ ID:3213, and is provided hereinbelow with reference to the sequence listing part.

[22787] VGAM502 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM502 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM502 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22788] VGAM502 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM502 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM502 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM502 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM502 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22789] The complementary binding of VGAM502 RNA, herein designated VGAM RNA, to host target binding sites on VGAM502 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM502 host target RNA into VGAM502 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22790] It is appreciated that VGAM502 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM502 host target genes. The mRNA of each one of this plurality of VGAM502 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM502 RNA, herein designated VGAM RNA, and which when bound by VGAM502 RNA causes inhibition of translation of respective one or more VGAM502 host target proteins.

[22791] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM502 gene, herein designated VGAM GENE, on one or more VGAM502 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22792] It is yet further appreciated that a function of VGAM502 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM502 include diagnosis, prevention and treatment of viral infection by Carrot Mottle Mimic Virus. Specific functions, and accordingly utilities, of VGAM502 correlate with, and may be deduced from, the identity of the host target genes which VGAM502 binds and inhibits,

and the function of these host target genes, as elaborated hereinbelow.

[22793] Nucleotide sequences of the VGAM502 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM502 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM502 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM502 are further described hereinbelow with reference to Table 1.

[22794] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM502 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM502 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22795] As mentioned hereinabove with reference to Fig. 1, a function of VGAM502 gene, herein designated VGAM is inhibition of expression of VGAM502 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM502 correlate with, and may be deduced from, the identity of the target genes which VGAM502 binds and inhibits, and the function of these target genes,



as elaborated hereinbelow.

[22796] CDC14 Cell Division Cycle 14 Homolog B (*S. cerevisiae*) (CDC14B, Accession NM\_033332) is a VGAM502 host target gene. CDC14B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDC14B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDC14B BINDING SITE, designated SEQ ID:27171, to the nucleotide sequence of VGAM502 RNA, herein designated VGAM RNA, also designated SEQ ID:3213.

[22797] A function of VGAM502 is therefore inhibition of CDC14 Cell Division Cycle 14 Homolog B (*S. cerevisiae*) (CDC14B, Accession NM\_033332). Accordingly, utilities of VGAM502 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDC14B. Lipoma HMGIC Fusion Partner-like 2 (LHFPL2, Accession XM\_046054) is another VGAM502 host target gene. LHFPL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LHFPL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of LHFPL2 BINDING SITE, designated SEQ ID:34661, to the nucleotide sequence of VGAM502 RNA, herein designated VGAM RNA, also designated SEQ ID:3213.

[22798] Another function of VGAM502 is therefore inhibition of Lipoma HMGIC Fusion Partner-like 2 (LHFPL2, Accession XM\_046054). Accordingly, utilities of VGAM502 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LHFPL2. LOC115343 (Accession XM\_050640) is another VGAM502 host target gene. LOC115343 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC115343, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115343 BINDING SITE, designated SEQ ID:35665, to the nucleotide sequence of VGAM502 RNA, herein designated VGAM RNA, also designated SEQ ID:3213.

[22799] Another function of VGAM502 is therefore inhibition of LOC115343 (Accession XM\_050640). Accordingly, utilities of VGAM502 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC115343. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 503 (VGAM503) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22800] VGAM503 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM503 was detected is described hereinabove with reference to Figs. 1–8.

[22801] VGAM503 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Molluscum Contagiosum Virus. VGAM503 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22802] VGAM503 gene encodes a VGAM503 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM503 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM503 precursor RNA is designated SEQ

ID:489, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:489 is located at position 9956 relative to the genome of Mollusc Contagiosum Virus.

[22803] VGAM503 precursor RNA folds onto itself, forming VGAM503 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22804] An enzyme complex designated DICER COMPLEX, `dices` the VGAM503 folded precursor RNA into VGAM503 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM503 RNA is designated SEQ ID:3214, and is provided hereinbelow with reference to the sequence

listing part.

[22805] VGAM503 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM503 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM503 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22806] VGAM503 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM503 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM503 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM503 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM503 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22807] The complementary binding of VGAM503 RNA, herein designated VGAM RNA, to host target binding sites on VGAM503 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM503 host target RNA into VGAM503 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22808] It is appreciated that VGAM503 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM503 host target genes. The mRNA of each one of this plurality of VGAM503 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM503 RNA, herein designated VGAM

RNA, and which when bound by VGAM503 RNA causes inhibition of translation of respective one or more VGAM503 host target proteins.

[22809] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM503 gene, herein designated VGAM GENE, on one or more VGAM503 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22810] It is yet further appreciated that a function of VGAM503 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM503 include diagnosis, prevention and treatment of viral infection by Mollusum Contagiosum Virus. Specific functions, and accordingly utilities, of VGAM503 correlate with, and may be deduced from, the identity of the host target genes which VGAM503 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22811] Nucleotide sequences of the VGAM503 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM503 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM503 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM503 are further described hereinbelow with reference to Table 1.

[22812] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM503 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM503 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22813] As mentioned hereinabove with reference to Fig. 1, a function of VGAM503 gene, herein designated VGAM is



inhibition of expression of VGAM503 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM503 correlate with, and may be deduced from, the identity of the target genes which VGAM503 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22814] A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 1 (ADAMTS1, Accession NM\_006988) is a VGAM503 host target gene. ADAMTS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAMTS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAMTS1 BINDING SITE, designated SEQ ID:13851, to the nucleotide sequence of VGAM503 RNA, herein designated VGAM RNA, also designated SEQ ID:3214.

[22815] A function of VGAM503 is therefore inhibition of A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 1 (ADAMTS1, Accession NM\_006988). Accordingly, utilities of VGAM503 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with ADAMTS1. Frizzled Homolog 8 (Drosophila) (FZD8, Accession NM\_031866) is another VGAM503 host target gene. FZD8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FZD8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FZD8 BINDING SITE, designated SEQ ID:25624, to the nucleotide sequence of VGAM503 RNA, herein designated VGAM RNA, also designated SEQ ID:3214.

[22816] Another function of VGAM503 is therefore inhibition of Frizzled Homolog 8 (Drosophila) (FZD8, Accession NM\_031866), a gene which may be involved in transduction and intercellular transmission of polarity information during tissue morphogenesis and/or in differentiated tissues. Accordingly, utilities of VGAM503 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FZD8. The function of FZD8 has been established by previous studies. Drosophila cuticle hairs are arranged in a defined polarity that is genetically controlled by 'frizzled,' a 7-transmembrane receptor with a large extracellular N-terminal cysteine-rich domain

(CRD). Members of the FZD family are receptors for secreted WNT glycoproteins (see OMIM Ref. No. 602863), which are involved in developmental control. FZD proteins transmit signals through the beta-catenin (CTNNB1; 116806) or JNK (e.g., JNK3; 602897) pathways. The selection of intracellular signaling cascade may be determined by different C-terminal motifs in FZD proteins. By searching an EST database for sequences homologous to mouse Fzd8, followed by PCR, screening genomic DNA, brain cDNA, and fetal cDNA libraries, and RT-PCR on fetal kidney cDNA, Saitoh et al. (2001) isolated a cDNA encoding human FZD8. Sequence analysis predicted that the 694-amino acid protein, which is 69% identical to FZD5 (OMIM Ref. No. 601723) and 95% identical to mouse Fzd8, contains an N-terminal signal peptide, a CRD, 7 trans-membrane domains, 3 N-linked glycosylation sites, and a C-terminal ser/thr-X-val motif, which is a binding site for scaffold proteins with multiple PDZ domains. Northern blot analysis revealed expression of a 4.0-kb FZD8 transcript that was most abundant in fetal kidney, followed by fetal brain and fetal lung. In adult tissue, FZD8 was expressed in kidney, heart, pancreas, and skeletal muscle. Based on its high degree of identity to the mouse se-

quence, Saitoh et al. (2001) predicted that FZD8 may also activate the CTNNB1–TCF signaling pathway, like mouse Fzd8.

[22817] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22818] Saitoh, T.; Hirai, M.; Katoh, M. : Molecular cloning and characterization of human Frizzled–8 gene on chromosome 10p11.2. *Int. Oncol.* 18: 991–996, 2001. 3. Wang, Y.; Macke, J. P.; Abella, B. S.; Andreasson, K.; Worley, P.; Gilbert, D. J.; Copeland, N. G.; Jenkins, N. A.; Nathans, J. : A large family of putative transmembrane receptors homologous to the product of the *Drosophila* tissue polarity gene frizzled. *J. Biol. Chem.* 271: 4468–4476, 1996. ; and

[22819] CREATION DATE.

[22820] Further studies establishing the function and utilities of FZD8 are found in John Hopkins OMIM database record ID 606146, and in cited publications numbered 6601 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Huntingtin (Huntington disease) (HD, Accession NM\_002111) is another VGAM503 host target gene. HD BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA en-

coded by HD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HD BINDING SITE, designated SEQ ID:7895, to the nucleotide sequence of VGAM503 RNA, herein designated VGAM RNA, also designated SEQ ID:3214.

[22821] Another function of VGAM503 is therefore inhibition of Huntingtin (Huntington disease) (HD, Accession NM\_002111). Accordingly, utilities of VGAM503 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HD. X-ray Repair Complementing Defective Repair In Chinese Hamster Cells 2 (XRCC2, Accession NM\_005431) is another VGAM503 host target gene. XRCC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XRCC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XRCC2 BINDING SITE, designated SEQ ID:11903, to the nucleotide sequence of VGAM503 RNA, herein designated VGAM RNA, also designated SEQ ID:3214.

[22822] Another function of VGAM503 is therefore inhibition of X-ray Repair Complementing Defective Repair In Chinese Hamster Cells 2 (XRCC2, Accession NM\_005431), a gene which involves in the homologous recombination repair (hrr) pathway of double-stranded dna. Accordingly, utilities of VGAM503 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XRCC2. The function of XRCC2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM241. Chromosome 20 Open Reading Frame 59 (C20orf59, Accession NM\_022082) is another VGAM503 host target gene. C20orf59 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf59, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf59 BINDING SITE, designated SEQ ID:22626, to the nucleotide sequence of VGAM503 RNA, herein designated VGAM RNA, also designated SEQ ID:3214.

[22823] Another function of VGAM503 is therefore inhibition of Chromosome 20 Open Reading Frame 59 (C20orf59, Ac-

cession NM\_022082). Accordingly, utilities of VGAM503 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf59. Tight Junction Protein 2 (zona occludens 2) (TJP2, Accession XM\_005446) is another VGAM503 host target gene. TJP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TJP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TJP2 BINDING SITE, designated SEQ ID:29980, to the nucleotide sequence of VGAM503 RNA, herein designated VGAM RNA, also designated SEQ ID:3214.

[22824] Another function of VGAM503 is therefore inhibition of Tight Junction Protein 2 (zona occludens 2) (TJP2, Accession XM\_005446). Accordingly, utilities of VGAM503 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TJP2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 504 (VGAM504) viral gene, which modulates expression of respective host target genes thereof, the function and utility

of which host target genes is known in the art.

[22825] VGAM504 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM504 was detected is described hereinabove with reference to Figs. 1–8.

[22826] VGAM504 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Mollusum Contagiosum Virus. VGAM504 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22827] VGAM504 gene encodes a VGAM504 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM504 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM504 precursor RNA is designated SEQ ID:490, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:490 is located at position 49770 relative to the genome of Mollusum Contagiosum Virus.

[22828] VGAM504 precursor RNA folds onto itself, forming VGAM504 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional



`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[22829] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM504 folded precursor RNA into VGAM504 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 70%) nucleotide se-  
quence of VGAM504 RNA is designated SEQ ID:3215, and  
is provided hereinbelow with reference to the sequence  
listing part.

[22830] VGAM504 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM504 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM504 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[22831] VGAM504 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM504 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM504 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM504 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM504 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[22832] The complementary binding of VGAM504 RNA, herein designated VGAM RNA, to host target binding sites on VGAM504 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM504 host target RNA into VGAM504 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22833] It is appreciated that VGAM504 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM504 host target genes. The mRNA of each one of this plurality of VGAM504 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM504 RNA, herein designated VGAM RNA, and which when bound by VGAM504 RNA causes inhibition of translation of respective one or more VGAM504 host target proteins.

[22834] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM504 gene, herein designated VGAM GENE, on one or

more VGAM504 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22835] It is yet further appreciated that a function of VGAM504 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM504 include diagnosis, prevention and treatment of viral infection by Molluscum Contagiosum Virus. Specific functions, and accordingly utilities, of VGAM504 correlate with, and may be deduced from, the identity of the host target genes which VGAM504 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22836] Nucleotide sequences of the VGAM504 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM504 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM504 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM504 are further described hereinbelow with reference to Table 1.

[22837] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM504 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM504 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22838] As mentioned hereinabove with reference to Fig. 1, a function of VGAM504 gene, herein designated VGAM is inhibition of expression of VGAM504 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM504 correlate with, and may be deduced from, the identity of the target genes which VGAM504 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22839] Nuclear Factor of Activated T-cells, Cytoplasmic, Cal-

calcineurin-dependent 1 (NFATC1, Accession NM\_006162) is a VGAM504 host target gene. NFATC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NFATC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFATC1 BINDING SITE, designated SEQ ID:12816, to the nucleotide sequence of VGAM504 RNA, herein designated VGAM RNA, also designated SEQ ID:3215.

[22840] A function of VGAM504 is therefore inhibition of Nuclear Factor of Activated T-cells, Cytoplasmic, Calcineurin-dependent 1 (NFATC1, Accession NM\_006162), a gene which regulates the activation, proliferation, differentiation and programmed death of lymphoid and nonlymphoid cells. Accordingly, utilities of VGAM504 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NFATC1. The function of NFATC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM123. Transducin (beta)-like 2 (TBL2, Accession NM\_032988) is another VGAM504 host target gene. TBL2 BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by TBL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBL2 BINDING SITE, designated SEQ ID:26871, to the nucleotide sequence of VGAM504 RNA, herein designated VGAM RNA, also designated SEQ ID:3215.

[22841] Another function of VGAM504 is therefore inhibition of Transducin (beta)-like 2 (TBL2, Accession NM\_032988), a gene which is of unknown function. Accordingly, utilities of VGAM504 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TBL2. The function of TBL2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM229.DKFZp586I021 (Accession NM\_032271) is another VGAM504 host target gene. DKFZp586I021 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp586I021, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of DKFZp586I021 BINDING SITE, designated SEQ ID:26022, to the nucleotide sequence of VGAM504 RNA, herein designated VGAM RNA, also designated SEQ ID:3215.

[22842] Another function of VGAM504 is therefore inhibition of DKFZp586I021 (Accession NM\_032271). Accordingly, utilities of VGAM504 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp586I021. FLJ22362 (Accession NM\_022823) is another VGAM504 host target gene. FLJ22362 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ22362, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22362 BINDING SITE, designated SEQ ID:23104, to the nucleotide sequence of VGAM504 RNA, herein designated VGAM RNA, also designated SEQ ID:3215.

[22843] Another function of VGAM504 is therefore inhibition of FLJ22362 (Accession NM\_022823). Accordingly, utilities of VGAM504 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22362. JM11 (Accession NM\_033626) is another VGAM504 host



target gene. JM11 BINDING SITE1 and JM11 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by JM11, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JM11 BINDING SITE1 and JM11 BINDING SITE2, designated SEQ ID:27328 and SEQ ID:27329 respectively, to the nucleotide sequence of VGAM504 RNA, herein designated VGAM RNA, also designated SEQ ID:3215.

[22844] Another function of VGAM504 is therefore inhibition of JM11 (Accession NM\_033626). Accordingly, utilities of VGAM504 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JM11. LOC96597 (Accession XM\_039922) is another VGAM504 host target gene. LOC96597 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC96597, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC96597 BINDING SITE, designated SEQ ID:33230, to the nucleotide sequence of VGAM504 RNA, herein designated VGAM RNA,

also designated SEQ ID:3215.

[22845] Another function of VGAM504 is therefore inhibition of LOC96597 (Accession XM\_039922). Accordingly, utilities of VGAM504 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC96597. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 505 (VGAM505) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22846] VGAM505 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM505 was detected is described hereinabove with reference to Figs. 1–8.

[22847] VGAM505 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Molluscum Contagiosum Virus. VGAM505 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22848] VGAM505 gene encodes a VGAM505 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM505 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM505 precursor RNA is designated SEQ ID:491, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:491 is located at position 106639 relative to the genome of Moluscum Contagiosum Virus.

[22849] VGAM505 precursor RNA folds onto itself, forming VGAM505 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22850] An enzyme complex designated DICER COMPLEX, `dices` the VGAM505 folded precursor RNA into VGAM505 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM505 RNA is designated SEQ ID:3216, and is provided hereinbelow with reference to the sequence listing part.

[22851] VGAM505 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM505 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM505 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22852] VGAM505 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM505 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM505 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM505 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM505 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22853] The complementary binding of VGAM505 RNA, herein designated VGAM RNA, to host target binding sites on VGAM505 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM505 host target RNA into VGAM505 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22854] It is appreciated that VGAM505 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM505 host target genes. The mRNA of

each one of this plurality of VGAM505 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM505 RNA, herein designated VGAM RNA, and which when bound by VGAM505 RNA causes inhibition of translation of respective one or more VGAM505 host target proteins.

[22855] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM505 gene, herein designated VGAM GENE, on one or more VGAM505 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[22856] It is yet further appreciated that a function of VGAM505 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of viral infection by Mollusum Contagiosum Virus. Specific functions, and accordingly utilities, of VGAM505 correlate with, and may be deduced from, the identity of the host target genes which VGAM505 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22857] Nucleotide sequences of the VGAM505 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM505 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM505 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM505 are further described hereinbelow with reference to Table 1.

[22858] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM505 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM505 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[22859] As mentioned hereinabove with reference to Fig. 1, a function of VGAM505 gene, herein designated VGAM is inhibition of expression of VGAM505 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM505 correlate with, and may be deduced from, the identity of the target genes which VGAM505 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22860] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3 (ABCC3, Accession NM\_020038) is a VGAM505 host target gene. ABCC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABCC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCC3 BINDING SITE, designated SEQ ID:21295, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22861] A function of VGAM505 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3



(ABCC3, Accession NM\_020038), a gene which may act as an inducible transporter in the biliary and intestinal excretion of organic anions. Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCC3. The function of ABCC3 has been established by previous studies. Bile secretion in liver is driven in large part by ATP-binding cassette (ABC)-type proteins that reside in the canalicular membrane and effect ATP-dependent transport of bile acids, phospholipids, and non-bile acid organic anions. Canalicular ABC-type proteins can be classified into 2 subfamilies based on membrane topology and sequence identity: MDR1 (multidrug resistance-1; 171050), MDR3 (multidrug resistance-3; 171060), and SPGP (bile salt export pump, or sister of P-glycoprotein; 603201) resemble the multidrug resistance P-glycoprotein, whereas MRP2 (OMIM Ref. No. 601107) is similar in structure and sequence to the multidrug resistance protein MRP1 (OMIM Ref. No. 158343) and transports similar substrates. Kool et al. (1999) detected expression of ABCC3 in the lateral side of cholangiocytes and in the basolateral membranes of hepatocytes, where it mediates transport of S-glutathione. When expressed in

ovarian carcinoma cells, ABCC3 conferred resistance to the anticancer drugs methotrexate, etoposide, and teniposide. The authors noted that sequence analysis of ABCC3 predicts a protein organized in a way similar to ABCC1 and ABCC2. Using FISH, Uchiumi et al. (1998) mapped the ABCC3 gene to 17q22.

[22862] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22863] Kool, M.; van der Linden, M.; de Haas, M.; Scheffer, G. L.; de Vree, J. M. L.; Smith, A. J.; Jansen, G.; Peters, G. J.; Ponne, N.; Scheper, R. J.; Oude Elferink, R. P. J.; Baas, F.; Borst, P. : MRP3, an organic anion transporter able to transport anti-cancer drugs. Proc. Nat. Acad. Sci. 96: 6914–6919, 1999. ; and

[22864] Uchiumi, T.; Hinoshita, E.; Haga, S.; Nakamura, T.; Tanaka, T.; Toh, S.; Furukawa, M.; Kawabe, T.; Wada, M.; Kagotani, K.; Okumura, K.; Kohno, K.; Akiyama, S.; Kuwano, M. : Isolation of.

[22865] Further studies establishing the function and utilities of ABCC3 are found in John Hopkins OMIM database record ID 604323, and in cited publications numbered 5013–501 and 7467 listed in the bibliography section hereinbelow,

which are also hereby incorporated by reference. SH3-domain Binding Protein 4 (SH3BP4, Accession NM\_014521) is another VGAM505 host target gene. SH3BP4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SH3BP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SH3BP4 BINDING SITE, designated SEQ ID:15856, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22866] Another function of VGAM505 is therefore inhibition of SH3-domain Binding Protein 4 (SH3BP4, Accession NM\_014521), a gene which is of unknown function, contains SH3-domain binding protein 4; similar to the EH-binding protein. Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SH3BP4. The function of SH3BP4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. Cofactor Required For Sp1 Transcriptional Acti-

vation, Subunit 3, 130kDa (CRSP3, Accession XM\_027112) is another VGAM505 host target gene. CRSP3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CRSP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRSP3 BINDING SITE, designated SEQ ID:30413, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22867] Another function of VGAM505 is therefore inhibition of Cofactor Required For Sp1 Transcriptional Activation, Subunit 3, 130kDa (CRSP3, Accession XM\_027112). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRSP3. Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665) is another VGAM505 host target gene. EVI5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by EVI5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVI5 BINDING SITE, designated SEQ ID:12211,

to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22868] Another function of VGAM505 is therefore inhibition of Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EVI5. FLJ14888 (Accession NM\_032856) is another VGAM505 host target gene. FLJ14888 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14888, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14888 BINDING SITE, designated SEQ ID:26657, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22869] Another function of VGAM505 is therefore inhibition of FLJ14888 (Accession NM\_032856). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14888. KIAA1058 (Accession XM\_090586) is another VGAM505 host target gene. KIAA1058 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by KIAA1058, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1058 BINDING SITE, designated SEQ ID:40013, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22870] Another function of VGAM505 is therefore inhibition of KIAA1058 (Accession XM\_090586). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1058. NBR2 (Accession NM\_005821) is another VGAM505 host target gene. NBR2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NBR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NBR2 BINDING SITE, designated SEQ ID:12425, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22871] Another function of VGAM505 is therefore inhibition of

NBR2 (Accession NM\_005821). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NBR2. PIP3-E (Accession XM\_039749) is another VGAM505 host target gene. PIP3-E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIP3-E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIP3-E BINDING SITE, designated SEQ ID:33174, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22872] Another function of VGAM505 is therefore inhibition of PIP3-E (Accession XM\_039749). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP3-E. LOC158969 (Accession XM\_088728) is another VGAM505 host target gene. LOC158969 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158969, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of LOC158969 BINDING SITE, designated SEQ ID:39923, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22873] Another function of VGAM505 is therefore inhibition of LOC158969 (Accession XM\_088728). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158969. LOC196510 (Accession XM\_113738) is another VGAM505 host target gene. LOC196510 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196510, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196510 BINDING SITE, designated SEQ ID:42396, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22874] Another function of VGAM505 is therefore inhibition of LOC196510 (Accession XM\_113738). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196510. LOC199986 (Accession XM\_117168) is an-



other VGAM505 host target gene. LOC199986 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199986, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199986 BINDING SITE, designated SEQ ID:43272, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22875] Another function of VGAM505 is therefore inhibition of LOC199986 (Accession XM\_117168). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199986. LOC200220 (Accession XM\_114157) is another VGAM505 host target gene. LOC200220 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200220, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200220 BINDING SITE, designated SEQ ID:42745, to the nucleotide sequence of VGAM505 RNA, herein designated VGAM RNA, also designated SEQ ID:3216.

[22876] Another function of VGAM505 is therefore inhibition of LOC200220 (Accession XM\_114157). Accordingly, utilities of VGAM505 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200220. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 506 (VGAM506) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22877] VGAM506 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM506 was detected is described hereinabove with reference to Figs. 1–8.

[22878] VGAM506 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saguaro Cactus Virus. VGAM506 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22879] VGAM506 gene encodes a VGAM506 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM506

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM506 precursor RNA is designated SEQ ID:492, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:492 is located at position 1711 relative to the genome of Saguaro Cactus Virus.

[22880] VGAM506 precursor RNA folds onto itself, forming VGAM506 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22881] An enzyme complex designated DICER COMPLEX, `dices` the VGAM506 folded precursor RNA into VGAM506 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 40%) nucleotide sequence of VGAM506 RNA is designated SEQ ID:3217, and is provided hereinbelow with reference to the sequence listing part.

[22882] VGAM506 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM506 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM506 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[22883] VGAM506 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM506 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM506 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM506 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM506 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22884] The complementary binding of VGAM506 RNA, herein designated VGAM RNA, to host target binding sites on VGAM506 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM506 host target RNA into VGAM506 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22885] It is appreciated that VGAM506 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM506 host target genes. The mRNA of each one of this plurality of VGAM506 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM506 RNA, herein designated VGAM RNA, and which when bound by VGAM506 RNA causes inhibition of translation of respective one or more VGAM506 host target proteins.

[22886] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM506 gene, herein designated VGAM GENE, on one or more VGAM506 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22887] It is yet further appreciated that a function of VGAM506 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM506 include diagnosis, prevention and treatment of viral infection by Saguaro Cactus Virus. Specific functions, and accordingly utilities, of VGAM506 correlate with, and may be deduced from, the identity of the host target genes which VGAM506 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22888] Nucleotide sequences of the VGAM506 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM506 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM506 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM506 are further described hereinbelow with reference to Table 1.

[22889] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM506 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM506 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[22890] As mentioned hereinabove with reference to Fig. 1, a function of VGAM506 gene, herein designated VGAM is inhibition of expression of VGAM506 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM506 correlate with, and may be deduced from, the identity of the target genes which VGAM506 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22891] ADP-ribosyltransferase (NAD<sup>+</sup>; poly (ADP-ribose) Polymerase) (ADPRT, Accession NM\_001618) is a VGAM506 host target gene. ADPRT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADPRT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADPRT BINDING SITE, designated SEQ ID:7323, to the nucleotide sequence of VGAM506 RNA, herein designated VGAM RNA, also designated SEQ ID:3217.

[22892] A function of VGAM506 is therefore inhibition of ADP-ribosyltransferase (NAD<sup>+</sup>; poly (ADP-ribose) Polymerase) (ADPRT, Accession NM\_001618), a gene which catalyzes



addition of mono-ADP-ribose to arginine residues of proteins, inhibits Pol II transcription. Accordingly, utilities of VGAM506 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADPRT. The function of ADPRT has been established by previous studies. The chromatin-associated enzyme poly(ADP-ribose) polymerase (ADPRT; EC 2.4.2.30) is a 116-kD protein that uses NAD as substrate to catalyze both the covalent transfer of ADP-ribose to a variety of nuclear protein acceptors and subsequently the transfer of an additional 60 to 80 ADP-ribose units to the initial moiety. Nuclear proteins that become predominantly poly(ADP-ribosyl)ated include nucleosomal core histones, histone H1 (see OMIM Ref. No. 142711), HMG proteins (see OMIM Ref. No. 163910), and topoisomerases I (OMIM Ref. No. 126420) and II (see OMIM Ref. No. 126430). ADP ribosyltransferase is required for cellular repair. Inhibitors of this enzyme potentiate the lethal effects of noxious agents. During repair, NAD(+) is consumed and the NAD(+) content of the cell decreases. Concomitantly, nuclear proteins are ADP-ribosylated. The enzyme is induced by single-strand breaks in DNA which serve as co-substrate for the reaction. Yu et al. (2002) demonstrated

that PARP1 activation is required for translocation of apoptosis-inducing factor (AIF; 300169) from the mitochondria to the nucleus and that AIF is necessary for PARP1-dependent cell death. N-methyl-N-prime-nitro-N-nitrosoguanidine, hydrogen peroxide, and NMDA induce AIF translocation and cell death, which is prevented by PARP inhibitors or genetic knockout of PARP1, but is caspase independent. Microinjection of an antibody to AIF protects against PARP1-dependent cytotoxicity. Yu et al. (2002) concluded that their data support a model in which PARP1 activation signals AIF release from mitochondria, resulting in a caspase-independent pathway of programmed cell death. Animal model experiments lend further support to the function of ADPRT. . Pieper et al. (1999) demonstrated DNA damage and a major activation of PARP in pancreatic islets of STZ-treated mice. These mice displayed a 5-fold increase in blood glucose and major pancreatic islet damage.

[22893] It is appreciated that the abovementioned animal model for ADPRT is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[22894] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22895] Yu, S.-W.; Wang, H.; Poitras, M. F.; Coombs, C.; Bowers, W. J.; Federoff, H. J.; Poirier, G. G.; Dawson, T. M.; Dawson, V. L. : Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor. Science 297: 259-263, 2002. ; and

[22896] Pieper, A. A.; Brat, D. J.; Krug, D. K.; Watkins, C. C.; Gupta, A.; Blackshaw, S.; Verma, A.; Wang, Z.-Q.; Snyder, S. H. : Poly(ADP-ribose) polymerase-deficient mice are protected from.

[22897] Further studies establishing the function and utilities of ADPRT are found in John Hopkins OMIM database record ID 173870, and in cited publications numbered 1772-1774, 1778-1777, 1779-1791, 2124, 420 and 10258-10261 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fibrinogen, A Alpha Polypeptide (FGA, Accession NM\_000508) is another VGAM506 host target gene. FGA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FGA, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGA BINDING SITE, designated SEQ ID:6120, to the nucleotide sequence of VGAM506 RNA, herein designated VGAM RNA, also designated SEQ ID:3217.

[22898] Another function of VGAM506 is therefore inhibition of Fibrinogen, A Alpha Polypeptide (FGA, Accession NM\_000508). Accordingly, utilities of VGAM506 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGA. KIAA0993 (Accession XM\_034413) is another VGAM506 host target gene. KIAA0993 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0993, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0993 BINDING SITE, designated SEQ ID:32079, to the nucleotide sequence of VGAM506 RNA, herein designated VGAM RNA, also designated SEQ ID:3217.

[22899] Another function of VGAM506 is therefore inhibition of KIAA0993 (Accession XM\_034413). Accordingly, utilities of VGAM506 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0993. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 507 (VGAM507) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22900] VGAM507 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM507 was detected is described hereinabove with reference to Figs. 1–8.

[22901] VGAM507 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saguaro Cactus Virus. VGAM507 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22902] VGAM507 gene encodes a VGAM507 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM507 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM507 precursor RNA is designated SEQ

ID:493, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:493 is located at position 2130 relative to the genome of Saguaro Cactus Virus.

[22903] VGAM507 precursor RNA folds onto itself, forming VGAM507 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22904] An enzyme complex designated DICER COMPLEX, `dices` the VGAM507 folded precursor RNA into VGAM507 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM507 RNA is designated SEQ ID:3218, and is provided hereinbelow with reference to the sequence

listing part.

[22905] VGAM507 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM507 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM507 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22906] VGAM507 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM507 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM507 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM507 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM507 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22907] The complementary binding of VGAM507 RNA, herein designated VGAM RNA, to host target binding sites on VGAM507 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM507 host target RNA into VGAM507 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22908] It is appreciated that VGAM507 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM507 host target genes. The mRNA of each one of this plurality of VGAM507 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM507 RNA, herein designated VGAM



RNA, and which when bound by VGAM507 RNA causes inhibition of translation of respective one or more VGAM507 host target proteins.

[22909] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM507 gene, herein designated VGAM GENE, on one or more VGAM507 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22910] It is yet further appreciated that a function of VGAM507 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM507 include diagnosis, prevention and treatment of viral infection by Saguaro Cactus Virus. Specific functions, and accordingly utilities, of VGAM507 correlate with, and may be deduced from, the identity of the host target genes which VGAM507 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22911] Nucleotide sequences of the VGAM507 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM507 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM507 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM507 are further described hereinbelow with reference to Table 1.

[22912] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM507 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM507 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22913] As mentioned hereinabove with reference to Fig. 1, a function of VGAM507 gene, herein designated VGAM is

inhibition of expression of VGAM507 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM507 correlate with, and may be deduced from, the identity of the target genes which VGAM507 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22914] Chromosome 20 Open Reading Frame 126 (C20orf126, Accession NM\_030815) is a VGAM507 host target gene. C20orf126 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf126, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf126 BINDING SITE, designated SEQ ID:25133, to the nucleotide sequence of VGAM507 RNA, herein designated VGAM RNA, also designated SEQ ID:3218.

[22915] A function of VGAM507 is therefore inhibition of Chromosome 20 Open Reading Frame 126 (C20orf126, Accession NM\_030815). Accordingly, utilities of VGAM507 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf126. Phosphatidylinositol-4-phosphate 5-kinase, Type II, Beta (PIP5K2B, Ac-

cession NM\_003559) is another VGAM507 host target gene. PIP5K2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIP5K2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIP5K2B BINDING SITE, designated SEQ ID:9615, to the nucleotide sequence of VGAM507 RNA, herein designated VGAM RNA, also designated SEQ ID:3218.

[22916] Another function of VGAM507 is therefore inhibition of Phosphatidylinositol-4-phosphate 5-kinase, Type II, Beta (PIP5K2B, Accession NM\_003559). Accordingly, utilities of VGAM507 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP5K2B. Zinc Finger, DHHC Domain Containing 2 (ZDHHC2, Accession NM\_016353) is another VGAM507 host target gene. ZDHHC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZDHHC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZDHHC2 BINDING SITE, designated SEQ

ID:18484, to the nucleotide sequence of VGAM507 RNA, herein designated VGAM RNA, also designated SEQ ID:3218.

[22917] Another function of VGAM507 is therefore inhibition of Zinc Finger, DHHC Domain Containing 2 (ZDHHC2, Accession NM\_016353). Accordingly, utilities of VGAM507 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZDHHC2. LOC150142 (Accession XM\_086791) is another VGAM507 host target gene. LOC150142 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150142 BINDING SITE, designated SEQ ID:38848, to the nucleotide sequence of VGAM507 RNA, herein designated VGAM RNA, also designated SEQ ID:3218.

[22918] Another function of VGAM507 is therefore inhibition of LOC150142 (Accession XM\_086791). Accordingly, utilities of VGAM507 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150142. LOC219988 (Accession XM\_166223) is an-

other VGAM507 host target gene. LOC219988 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219988, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219988 BINDING SITE, designated SEQ ID:44046, to the nucleotide sequence of VGAM507 RNA, herein designated VGAM RNA, also designated SEQ ID:3218.

[22919] Another function of VGAM507 is therefore inhibition of LOC219988 (Accession XM\_166223). Accordingly, utilities of VGAM507 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219988. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 508 (VGAM508) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22920] VGAM508 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM508 was detected is described

hereinabove with reference to Figs. 1–8.

[22921] VGAM508 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saguaro Cactus Virus. VGAM508 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22922] VGAM508 gene encodes a VGAM508 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM508 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM508 precursor RNA is designated SEQ ID:494, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:494 is located at position 1022 relative to the genome of Saguaro Cactus Virus.

[22923] VGAM508 precursor RNA folds onto itself, forming VGAM508 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22924] An enzyme complex designated DICER COMPLEX, `dices` the VGAM508 folded precursor RNA into VGAM508 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM508 RNA is designated SEQ ID:3219, and is provided hereinbelow with reference to the sequence listing part.

[22925] VGAM508 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM508 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM508 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22926] VGAM508 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-



cated in untranslated regions of VGAM508 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM508 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM508 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM508 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22927] The complementary binding of VGAM508 RNA, herein designated VGAM RNA, to host target binding sites on VGAM508 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM508 host target RNA into VGAM508 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22928] It is appreciated that VGAM508 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM508 host target genes. The mRNA of each one of this plurality of VGAM508 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM508 RNA, herein designated VGAM RNA, and which when bound by VGAM508 RNA causes inhibition of translation of respective one or more VGAM508 host target proteins.

[22929] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM508 gene, herein designated VGAM GENE, on one or more VGAM508 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22930] It is yet further appreciated that a function of VGAM508 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of viral infection by Saguaro Cactus Virus. Specific functions, and accordingly utilities, of VGAM508 correlate with, and may be deduced from, the identity of the host target genes which VGAM508 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22931] Nucleotide sequences of the VGAM508 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM508 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM508 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM508 are further described hereinbelow with reference to Table 1.

[22932] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM508 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM508 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22933] As mentioned hereinabove with reference to Fig. 1, a function of VGAM508 gene, herein designated VGAM is inhibition of expression of VGAM508 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM508 correlate with, and may be deduced from, the identity of the target genes which VGAM508 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22934] A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 3 (ADAMTS3, Accession NM\_014243) is a VGAM508 host target gene. ADAMTS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

ADAMTS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAMTS3 BINDING SITE, designated SEQ ID:15508, to the nucleotide sequence of VGAM508 RNA, herein designated VGAM RNA, also designated SEQ ID:3219.

[22935] A function of VGAM508 is therefore inhibition of A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 3 (ADAMTS3, Accession NM\_014243), a gene which cleaves the propeptides of type ii collagen prior to fibril assembly. Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAMTS3. The function of ADAMTS3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM211. Carbonic Anhydrase XII (CA12, Accession NM\_001218) is another VGAM508 host target gene. CA12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CA12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of CA12 BINDING SITE, designated SEQ ID:6877, to the nucleotide sequence of VGAM508 RNA, herein designated VGAM RNA, also designated SEQ ID:3219.

[22936] Another function of VGAM508 is therefore inhibition of Carbonic Anhydrase XII (CA12, Accession NM\_001218), a gene which functions in cellular transport and metabolic processes. Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CA12. The function of CA12 has been established by previous studies. Tureci et al. (1998) cloned the gene identified by Sahin et al. (1995) from the RCC and named it CA XII. The cDNA sequence encodes a deduced 354-amino acid protein with a predicted molecular mass of 39,448 Da and features of a type I membrane protein. The extracellular CA domain shows 30 to 42% similarity with known human CAs, contains all 3 zinc-binding histidine residues found in active CAs, and contains 2 potential sites for asparagine glycosylation. Expression of the CA XII cDNA in mammalian cells produced a 43- to 44-kD doublet; treatment with PNGase (endoglycosidase) F resulted in a single 39-kD

product. The recombinant CA XII had appreciable catalytic activity. By Northern blot analysis, the authors detected a 4.5-kb CA XII transcript in normal human kidney, colon, and activated lymphocytes. They found that CA XII is overexpressed in 10% of clear cell renal carcinomas, as compared with the corresponding normal renal tissue. Sequencing revealed no differences between the RCC-derived cDNA and a CA XII cDNA isolated from normal kidney. Carbonic anhydrases (CAs) are a family of zinc metalloenzymes. For background information on the CA family,

[22937] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22938] Tureci, O.; Sahin, U.; Vollmar, E.; Siemer, S.; Gottert, E.; Seitz, G.; Parkkila, A. K.; Shah, G. N.; Grubb, J. H.; Pfrendschuh, M.; Sly, W. S. : Human carbonic anhydrase XII: cDNA cloning, expression, and chromosomal localization of a carbonic anhydrase gene that is overexpressed in some renal cell cancers. Proc. Nat. Acad. Sci. 95: 7608–7613, 1998. ; and

[22939] Sahin, U.; Tureci, O.; Schmitt, H.; Cochlovius, B.; Johannes, T.; Schmits, R.; Stenner, F.; Luo, G.; Schobert, I.; Pfrend-

schuh, M. : Human neoplasms elicit multiple specific immune resp.

[22940] Further studies establishing the function and utilities of CA12 are found in John Hopkins OMIM database record ID 603263, and in cited publications numbered 269 and 6327–6328 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cytochrome P450, Subfamily XIX (aromatization of androgens) (CYP19, Accession NM\_000103) is another VGAM508 host target gene. CYP19 BINDING SITE1 and CYP19 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CYP19, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP19 BINDING SITE1 and CYP19 BINDING SITE2, designated SEQ ID:5559 and SEQ ID:25269 respectively, to the nucleotide sequence of VGAM508 RNA, herein designated VGAM RNA, also designated SEQ ID:3219.

[22941] Another function of VGAM508 is therefore inhibition of Cytochrome P450, Subfamily XIX (aromatization of androgens) (CYP19, Accession NM\_000103), a gene which cat-



analyzes the last steps of estrogen biosynthesis. Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP19. The function of CYP19 has been established by previous studies. The distinct gender-specific patterns of fat distribution in men and women (android and gynoid) suggest a role for sex steroids. It has been suggested that estrogens can promote preadipocyte cell proliferation and/or differentiation. The enzyme CYP19 is responsible for the conversion of androgen precursor steroids to estrogens and may, therefore, have a role in regulating adipose tissue mass and its distribution. McTernan et al. (2002) investigated the glucocorticoid regulation of aromatase expression in adipose tissue, specifically to define any site- and gender-specific differences. Abdominal subcutaneous and omental adipose tissue was obtained from male and female patients undergoing elective surgery. Cortisol-induced aromatase activity in omental adipocytes from postmenopausal females was higher than that in premenopausal females ( $P$  less than 0.001). Insulin had no independent effect on aromatase expression, but coincubation of preadipocytes with cortisol and insulin eliminated both gender- and site-specific differ-

ences. The authors concluded that in women, but not men, cortisol increases aromatase activity at subcutaneous sites, and this may facilitate predilection for subcutaneous adiposity in females. They suggested that the observed site-, gender-, and menopausal-specific differences in the glucocorticoid regulation of this enzyme may contribute to the gender- and menopausal-specific patterns of fat distribution. Hemsell et al. (1977) reported a case of gynecomastia apparently due to excessive peripheral conversion of androgen to estrogen as a result of 50-times-normal aromatase activity. The patient was an adopted boy, aged 11 years 7 months. Effects of excessive estrogen became evident at age 8, the time when plasma androstenedione begins to increase. Extraglandular aromatization, as well as sulfurylation, is extensively involved in C19-steroid metabolism in the fetus, but the activity of the enzymes falls rapidly after birth. In the patient of Hemsell et al. (1977), the fetal situation appeared to persist. Berkovitz et al. (1985) investigated a black family in which marked gynecomastia with normal male genitalia occurred in 5 men in 3 sibships of 2 generations connected through females. In each, gynecomastia and male sexual differentiation began at an early age (10 to 11

years). The ratio of the concentration of plasma estradiol-17 beta to that of plasma testosterone was elevated in each. In 3 affected sibs, the transfer constant of conversion of androstenedione to estrone (i.e., the fraction of plasma androstenedione that was converted to estrone as measured in the urine) was 10 times the normal. Despite elevated extraglandular aromatase activity, the hypothalamic-pituitary axis responded normally to provocative stimuli. None of the 5 males had children, but 4 were still in their teens; the fifth was 29 years of age. The pattern of inheritance of familial gynecomastia with increased aromatase activity is consistent with either X-linked recessive or autosomal dominant, male-limited inheritance. Mapping of the aromatase locus to an autosome makes the latter possibility highly likely. Autosomal dominant inheritance appeared likely in a family, reported by Leiberman and Zachmann (1992), in which increased steroid aromatization seemed to be responsible for 'familial adrenal feminization.' The father and 2 male and 2 female sibs had gynecomastia, early growth, and short final stature. The 8-year-old propositus had advanced bone age, facial acne, gynecomastia, pubic hair, and prepubertal testicular volume. ACTH-dependent adrenal feminization was con-

firmed by a transient reduction of breast tissue following dexamethasone or cyproterone acetate treatment.

Testolactone, which is an inhibitor of peripheral aromatase activity in vivo, temporarily reduced the breast tissue. This was the first example of male-to-male and male-to-female transmission reported. Animal model experiments lend further support to the function of CYP19.

Aromatase knockout (ArKO) mice, lacking a functional Cyp19 gene, cannot synthesize endogenous estrogens.

Jones et al. (2000) examined the adipose deposits of male and female ArKO mice, observing that these animals progressively accumulated significantly more intraabdominal adipose tissue than their wildtype littermates, reflected in increased adipocyte volume at gonadal and infrarenal sites. This increased adiposity was not due to hyperphagia or reduced resting energy expenditure, but was associated with reduced spontaneous physical activity levels, reduced glucose oxidation, and a decrease in lean body mass. A striking accumulation of lipid droplets was observed in the livers of ArKO animals. The findings demonstrated an important role for estrogen in the maintenance of lipid homeostasis in both males and females. Along the same lines, Heine et al. (2000) studied male and female

Esr1 knockout mice and found that signaling by this receptor is critical in female and male white adipose tissue. Obesity in the males involved a mechanism of reduced energy expenditure rather than increased energy intake.

[22942] It is appreciated that the abovementioned animal model for CYP19 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[22943] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22944] Deladoey, J.; Fluck, C.; Bex, M.; Yoshimura, N.; Harada, N.; Mullis, P. E. : Aromatase deficiency caused by a novel P450(arom) gene mutation: impact of absent estrogen production on serum gonadotropin concentration in a boy. J. Clin. Endocr. Metab. 84: 4050–4054, 1999. ; and

[22945] Yang, S.; Fang, Z.; Suzuki, T.; Sasano, H.; Zhou, J.; Gurates, B.; Tamura, M.; Ferrer, K.; Bulun, S. : Regulation of aromatase P450 expression in endometriotic and endometrial stromal.

[22946] Further studies establishing the function and utilities of CYP19 are found in John Hopkins OMIM database record ID 107910, and in cited publications numbered 4675,

4845, 4855–4869, 2149, 4870–4871, 877, 4872–4881, 29, 12529–12530, 313 and 12531–12535 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Selectin E (endothelial adhesion molecule 1) (SELE, Accession NM\_000450) is another VGAM508 host target gene. SELE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SELE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SELE BINDING SITE, designated SEQ ID:6051, to the nucleotide sequence of VGAM508 RNA, herein designated VGAM RNA, also designated SEQ ID:3219.

[22947] Another function of VGAM508 is therefore inhibition of Selectin E (endothelial adhesion molecule 1) (SELE, Accession NM\_000450), a gene which expressed on cytokine induced endothelial cells and mediates their binding to leukocytes. Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SELE. The function of SELE has been established by previous studies. Zheng et al. (2001) examined whether a polymorphism in the SELE gene, due

to a G-to-T mutation (98G-T) in the untranslated region of exon 2, was related to premature coronary artery disease (CAD). Both lipid and nonlipid risk factors, including the ser128-to-arg substitution studied by Wenzel et al. (1994), were also assessed. The frequency of the 98G-T mutation was found to be significantly increased among male patients under 45 years of age and female patients under 55 years of age. After controlling for other CAD risk factors by multiple logistic analysis, the 98G-T mutation was still a significant predictor of premature CAD. The glaucomas are a group of optic neuropathies comprising the leading cause of irreversible blindness worldwide. Elevated intraocular pressure due to a reduction in normal aqueous outflow is a major causal risk factor. Wang et al. (2001) found that ELAM1, the earliest marker for the atherosclerotic plaque in the vasculature, was consistently present on trabecular meshwork cells in the outflow pathways of eyes with glaucomas of diverse etiology. They determined expression of ELAM1 to be controlled by activation of an interleukin-1 (see OMIM Ref. No. 147760) autocrine feedback loop through transcription factor NK-kappa-B (see OMIM Ref. No. 164011), and activity of this signaling pathway was shown to protect trabecular mesh-

work cells against oxidative stress. Wang et al. (2001) concluded that their findings characterized a protective stress response specific to the eye's aqueous outflow pathways and provided the first known diagnostic indicator of glaucomatous trabecular meshwork cells. They further indicated that common mechanisms contribute to the pathophysiology of the glaucomas and vascular diseases.

[22948] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22949] Wang, N.; Chintala, S. K.; Fini, M. E.; Schuman, J. S. : Activation of a tissue-specific stress response in the aqueous outflow pathway of the eye defines the glaucoma disease phenotype. *Nature Med.* 7: 304–309, 2001. ; and

[22950] Zheng, F.; Chevalier, J. A.; Zhang, L. Q.; Virgil, D.; Ye, S. Q.; Kwiterovich, P. O. : An HphI polymorphism in the E-selectin gene is associated with premature coronary artery diseases.

[22951] Further studies establishing the function and utilities of SELE are found in John Hopkins OMIM database record ID 131210, and in cited publications numbered 11805–11812 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer–



ence.FLJ21945 (Accession NM\_025203) is another VGAM508 host target gene. FLJ21945 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21945, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21945 BINDING SITE, designated SEQ ID:24866, to the nucleotide sequence of VGAM508 RNA, herein designated VGAM RNA, also designated SEQ ID:3219.

[22952] Another function of VGAM508 is therefore inhibition of FLJ21945 (Accession NM\_025203). Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21945. Heterogeneous Nuclear Ribonucleoprotein U (scaffold attachment factor A) (HNRPU, Accession NM\_031844) is another VGAM508 host target gene. HNRPU BINDING SITE1 and HNRPU BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HNRPU, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HNRPU BINDING SITE1 and HNRPU BINDING

SITE2, designated SEQ ID:25579 and SEQ ID:10835 respectively, to the nucleotide sequence of VGAM508 RNA, herein designated VGAM RNA, also designated SEQ ID:3219.

[22953] Another function of VGAM508 is therefore inhibition of Heterogeneous Nuclear Ribonucleoprotein U (scaffold attachment factor A) (HNRPU, Accession NM\_031844). Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HNRPU. LOC91266 (Accession XM\_037268) is another VGAM508 host target gene. LOC91266 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91266, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91266 BINDING SITE, designated SEQ ID:32600, to the nucleotide sequence of VGAM508 RNA, herein designated VGAM RNA, also designated SEQ ID:3219.

[22954] Another function of VGAM508 is therefore inhibition of LOC91266 (Accession XM\_037268). Accordingly, utilities of VGAM508 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC91266. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 509 (VGAM509) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22955] VGAM509 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM509 was detected is described hereinabove with reference to Figs. 1–8.

[22956] VGAM509 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Papaya Ringspot Virus. VGAM509 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22957] VGAM509 gene encodes a VGAM509 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM509 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM509 precursor RNA is designated SEQ ID:495, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:495 is located at position 7642 relative to the genome of Papaya Ringspot Virus.

[22958] VGAM509 precursor RNA folds onto itself, forming VGAM509 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22959] An enzyme complex designated DICER COMPLEX, `dices` the VGAM509 folded precursor RNA into VGAM509 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM509 RNA is designated SEQ ID:3220, and is provided hereinbelow with reference to the sequence listing part.

[22960] VGAM509 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM509 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM509 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[22961] VGAM509 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM509 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM509 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM509 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM509 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[22962] The complementary binding of VGAM509 RNA, herein designated VGAM RNA, to host target binding sites on VGAM509 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM509 host target RNA into VGAM509 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22963] It is appreciated that VGAM509 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM509 host target genes. The mRNA of each one of this plurality of VGAM509 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM509 RNA, herein designated VGAM RNA, and which when bound by VGAM509 RNA causes in-

hibition of translation of respective one or more VGAM509 host target proteins.

[22964] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM509 gene, herein designated VGAM GENE, on one or more VGAM509 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22965] It is yet further appreciated that a function of VGAM509 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM509 include diagnosis, prevention and

treatment of viral infection by Papaya Ringspot Virus. Specific functions, and accordingly utilities, of VGAM509 correlate with, and may be deduced from, the identity of the host target genes which VGAM509 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[22966] Nucleotide sequences of the VGAM509 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM509 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM509 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM509 are further described hereinbelow with reference to Table 1.

[22967] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM509 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM509 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22968] As mentioned hereinabove with reference to Fig. 1, a function of VGAM509 gene, herein designated VGAM is inhibition of expression of VGAM509 target genes. It is



appreciated that specific functions, and accordingly utilities, of VGAM509 correlate with, and may be deduced from, the identity of the target genes which VGAM509 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[22969] Cystinosis, Nephropathic (CTNS, Accession NM\_004937) is a VGAM509 host target gene. CTNS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CTNS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CTNS BINDING SITE, designated SEQ ID:11382, to the nucleotide sequence of VGAM509 RNA, herein designated VGAM RNA, also designated SEQ ID:3220.

[22970] A function of VGAM509 is therefore inhibition of Cystinosis, Nephropathic (CTNS, Accession NM\_004937). Accordingly, utilities of VGAM509 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CTNS. Mannosyl (alpha-1,6)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession NM\_002408) is another VGAM509 host target gene. MGAT2 BINDING SITE is HOST TARGET binding site

found in the 5' untranslated region of mRNA encoded by MGAT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAT2 BINDING SITE, designated SEQ ID:8231, to the nucleotide sequence of VGAM509 RNA, herein designated VGAM RNA, also designated SEQ ID:3220.

[22971] Another function of VGAM509 is therefore inhibition of Mannosyl (alpha-1,6-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession NM\_002408). Accordingly, utilities of VGAM509 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGAT2. HT001 (Accession XM\_039534) is another VGAM509 host target gene. HT001 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HT001, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HT001 BINDING SITE, designated SEQ ID:33115, to the nucleotide sequence of VGAM509 RNA, herein designated VGAM RNA, also designated SEQ

ID:3220.

[22972] Another function of VGAM509 is therefore inhibition of HT001 (Accession XM\_039534). Accordingly, utilities of VGAM509 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HT001. Zinc Finger Protein 226 (ZNF226, Accession NM\_016444) is another VGAM509 host target gene. ZNF226 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZNF226, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF226 BINDING SITE, designated SEQ ID:18565, to the nucleotide sequence of VGAM509 RNA, herein designated VGAM RNA, also designated SEQ ID:3220.

[22973] Another function of VGAM509 is therefore inhibition of Zinc Finger Protein 226 (ZNF226, Accession NM\_016444). Accordingly, utilities of VGAM509 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF226. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 510 (VGAM510) viral gene,

which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[22974] VGAM510 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM510 was detected is described hereinabove with reference to Figs. 1–8.

[22975] VGAM510 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Papaya Ringspot Virus. VGAM510 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[22976] VGAM510 gene encodes a VGAM510 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM510 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM510 precursor RNA is designated SEQ ID:496, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:496 is located at position 4216 relative to the genome of Papaya Ringspot Virus.

[22977] VGAM510 precursor RNA folds onto itself, forming

VGAM510 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[22978] An enzyme complex designated DICER COMPLEX, `dices` the VGAM510 folded precursor RNA into VGAM510 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM510 RNA is designated SEQ ID:3221, and is provided hereinbelow with reference to the sequence listing part.

[22979] VGAM510 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM510 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM510 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[22980] VGAM510 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM510 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM510 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM510 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM510 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[22981] The complementary binding of VGAM510 RNA, herein designated VGAM RNA, to host target binding sites on VGAM510 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM510 host target RNA into VGAM510 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[22982] It is appreciated that VGAM510 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM510 host target genes. The mRNA of each one of this plurality of VGAM510 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM510 RNA, herein designated VGAM RNA, and which when bound by VGAM510 RNA causes inhibition of translation of respective one or more VGAM510 host target proteins.

[22983] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM510 gene, herein designated VGAM GENE, on one or more VGAM510 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[22984] It is yet further appreciated that a function of VGAM510 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM510 include diagnosis, prevention and treatment of viral infection by Papaya Ringspot Virus. Specific functions, and accordingly utilities, of VGAM510 correlate with, and may be deduced from, the identity of the host target genes which VGAM510 binds and inhibits, and



the function of these host target genes, as elaborated hereinbelow.

[22985] Nucleotide sequences of the VGAM510 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM510 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM510 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM510 are further described hereinbelow with reference to Table 1.

[22986] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM510 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM510 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[22987] As mentioned hereinabove with reference to Fig. 1, a function of VGAM510 gene, herein designated VGAM is inhibition of expression of VGAM510 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM510 correlate with, and may be deduced from, the identity of the target genes which VGAM510 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[22988] B-cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898) is a VGAM510 host target gene. BCL11B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL11B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL11B BINDING SITE, designated SEQ ID:23157, to the nucleotide sequence of VGAM510 RNA, herein designated VGAM RNA, also designated SEQ ID:3221.

[22989] A function of VGAM510 is therefore inhibition of B-cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898). Accordingly, utilities of VGAM510 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL11B. Empty Spiracles Homolog 2 (Drosophila) (EMX2, Accession XM\_113640) is another VGAM510 host target gene. EMX2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EMX2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of EMX2 BINDING SITE, designated SEQ ID:42315, to the nucleotide sequence of VGAM510 RNA, herein designated VGAM RNA, also designated SEQ ID:3221.

[22990] Another function of VGAM510 is therefore inhibition of Empty Spiracles Homolog 2 (Drosophila) (EMX2, Accession XM\_113640), a gene which may function in combinations with otx1/2 to specify cell fates in the developing central nervous system. Accordingly, utilities of VGAM510 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EMX2. The function of EMX2 has been established by previous studies. Brunelli et al. (1996) described schizencephaly (OMIM Ref. No. 269160) as an extremely rare congenital disorder characterized by a full-thickness cleft within the cerebral hemispheres. The clefts are lined with gray matter and most commonly involve the parasylvian regions (Wolpert and Barnes, 1992). Large portions of the cerebral hemispheres may be absent and replaced by cerebrospinal fluid. In a search for mutations in the human homologs of the Emx1, Emx2, Otx1, and Otx2 genes, which are expressed in the developing mouse forebrain, Brunelli et al. (1996) found that 3 of 8 patients with severe schizencephaly were het-

erozygous for different mutations in the EMX2 gene. One of the mutations was a frameshift in the homeodomain resulting in the alteration of its carboxy terminus, including the entire recognition helix. The other 2 were 3-prime splice site mutations in the first intron, upstream from the homeodomain, which prevented appropriate splicing of EMX2 transcripts in vitro. All 3 were de novo mutations, as they were not present in the patients' parents. Thus, the authors concluded that the EMX2 protein appears to be required for the correct formation of the human cerebral cortex. Two types of schizencephaly have been described, depending on the size of the area involved and the separation of the cleft lips (Wolpert and Barnes, 1992). Type I schizencephaly consists of a fused cleft. This fused pial-apendymal seam forms a furrow in the developing brain, and is lined by polymicrogyric gray matter. In type II schizencephaly, there is a large defect, a holohemispheric cleft in the cerebral cortex filled with fluid and lined by polymicrogyric gray matter. The clinical manifestations depend on the severity of the lesion. Patients with type I are often almost normal; they may have seizures and spasticity. In type II abnormalities, there is usually mental retardation, seizures, hypotonia, spasticity, inability to

walk or speak, and blindness. The patients in whom Brunelli et al. (1996) demonstrated EMX2 mutations belonged to the type II category. The authors speculated that EMX2 may play a part in the control of cell proliferation of cortical neuroblasts and/or cell migration of postmitotic neurons, as it is known that these cells reach their final destination in the mature cortex according to their birth date (Boncinelli et al., 1995). Patients with mild forms of schizencephaly are often almost normal but may show partial epileptic seizures and mild spastic hemiparesis. Conversely, patients with bilateral open-lip clefts usually have microcephaly, severe developmental delay with serious mental retardation, and spastic quadriparesis. Adding to the previously reported analysis of EMX2 mutations in 7 of 8 sporadic cases of schizencephaly, Faiella et al. (1997) analyzed 10 additional patients, including 2 brothers. Six patients were found to be heterozygous for de novo mutations in EMX2. In particular, the 2 brothers, who had severe bilateral schizencephaly, showed the same mutation affecting the splicing of the first intron, while this mutation was absent in their parents and in 2 unaffected sibs. Presumably this was an instance of germinal mosaicism in one or the other of the parents. Some other patients with

mutations had mild unilateral schizencephaly associated with partial epilepsy. Mutation analysis by Noonan et al. (2001) of endometrioid adenocarcinomas and a Mullerian mesodermal tumor identified multiple variants in the EMX2 gene, including somatic mutations not found in normal DNA, intronic polymorphisms present in normal DNA samples, and polymorphisms in the 3-prime untranslated region. Noonan et al. (2001) concluded that EMX2 is most likely involved in the control of differentiation and possibly in tumor suppression. Animal model experiments lend further support to the function of EMX2. The contribution of extrinsic and genetic mechanisms in determining areas of the mammalian neocortex has been a contested issue. Bishop et al. (2000) analyzed the roles of the regulatory genes Emx2 and Pax6 (OMIM Ref. No. 607108), which are expressed in opposing gradients in the neocortical ventricular zone, in specifying areas. Changes in the patterning of molecular markers and area-specific connections between the cortex and thalamus suggested that arealization of the neocortex is disproportionately altered in Emx2 and Pax6 mutant mice in opposing manners predicted from their countergradients of expression: rostral areas expanded and caudal areas con-

tracted in Emx2 mutants, whereas the opposite effect was seen in Pax6 mutants. Bishop et al. (2000) concluded that Emx2 and Pax6 cooperate to regulate arealization of the neocortex and to confer area identity to cortical cells.

[22991] It is appreciated that the abovementioned animal model for EMX2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[22992] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[22993] Bishop, K. M.; Goudreau, G.; O'Leary, D. D. M. : Regulation of area identity in the mammalian neocortex by Emx2 and Pax6. Science 288: 344–349, 2000. ; and

[22994] Noonan, F. C.; Mutch, D. G.; Mallon, M. A.; Goodfellow, P. J. : Characterization of the homeodomain gene EMX2: sequence conservation, expression analysis, and a search for mutations in.

[22995] Further studies establishing the function and utilities of EMX2 are found in John Hopkins OMIM database record ID 600035, and in sited publications numbered 8112–8114, 8714, 925 and 8115 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer–

ence.PRO2086 (Accession NM\_014111) is another VGAM510 host target gene. PRO2086 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO2086, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2086 BINDING SITE, designated SEQ ID:15344, to the nucleotide sequence of VGAM510 RNA, herein designated VGAM RNA, also designated SEQ ID:3221.

[22996] Another function of VGAM510 is therefore inhibition of PRO2086 (Accession NM\_014111). Accordingly, utilities of VGAM510 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2086. Ubiquitin-like, Containing PHD and RING Finger Domains, 1 (UHRF1, Accession NM\_013282) is another VGAM510 host target gene. UHRF1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by UHRF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UHRF1 BINDING SITE, designated SEQ ID:14953, to the nucleotide sequence of



VGAM510 RNA, herein designated VGAM RNA, also designated SEQ ID:3221.

[22997] Another function of VGAM510 is therefore inhibition of Ubiquitin-like, Containing PHD and RING Finger Domains, 1 (UHRF1, Accession NM\_013282). Accordingly, utilities of VGAM510 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UHRF1. LOC139331 (Accession XM\_066631) is another VGAM510 host target gene. LOC139331 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC139331, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC139331 BINDING SITE, designated SEQ ID:37340, to the nucleotide sequence of VGAM510 RNA, herein designated VGAM RNA, also designated SEQ ID:3221.

[22998] Another function of VGAM510 is therefore inhibition of LOC139331 (Accession XM\_066631). Accordingly, utilities of VGAM510 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC139331. LOC151248 (Accession XM\_087143) is another VGAM510 host target gene. LOC151248 BINDING

SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151248, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151248 BINDING SITE, designated SEQ ID:39081, to the nucleotide sequence of VGAM510 RNA, herein designated VGAM RNA, also designated SEQ ID:3221.

[22999] Another function of VGAM510 is therefore inhibition of LOC151248 (Accession XM\_087143). Accordingly, utilities of VGAM510 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151248. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 511 (VGAM511) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23000] VGAM511 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM511 was detected is described hereinabove with reference to Figs. 1-8.

[23001] VGAM511 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cucumber Green Mottle Mosaic Virus. VGAM511 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23002] VGAM511 gene encodes a VGAM511 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM511 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM511 precursor RNA is designated SEQ ID:497, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:497 is located at position 1481 relative to the genome of Cucumber Green Mottle Mosaic Virus.

[23003] VGAM511 precursor RNA folds onto itself, forming VGAM511 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[23004] An enzyme complex designated DICER COMPLEX, `dices` the VGAM511 folded precursor RNA into VGAM511 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM511 RNA is designated SEQ ID:3222, and is provided hereinbelow with reference to the sequence listing part.

[23005] VGAM511 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM511 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM511 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23006] VGAM511 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM511 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM511 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM511 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM511 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23007] The complementary binding of VGAM511 RNA, herein designated VGAM RNA, to host target binding sites on VGAM511 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM511 host target RNA into VGAM511 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23008] It is appreciated that VGAM511 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM511 host target genes. The mRNA of each one of this plurality of VGAM511 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM511 RNA, herein designated VGAM RNA, and which when bound by VGAM511 RNA causes inhibition of translation of respective one or more VGAM511 host target proteins.

[23009] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM511 gene, herein designated VGAM GENE, on one or more VGAM511 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23010] It is yet further appreciated that a function of VGAM511 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of viral infection by Cucumber Green Mottle Mosaic Virus. Specific functions, and accordingly utilities, of VGAM511 correlate with, and may be deduced from, the identity of the host target genes which VGAM511 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23011] Nucleotide sequences of the VGAM511 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM511 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM511 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM511 are further described hereinbelow with reference to Table 1.

[23012] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM511 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM511 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23013] As mentioned hereinabove with reference to Fig. 1, a function of VGAM511 gene, herein designated VGAM is inhibition of expression of VGAM511 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM511 correlate with, and may be deduced from, the identity of the target genes which VGAM511 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23014] Cadherin 6, Type 2, K-cadherin (fetal kidney) (CDH6, Accession NM\_004932) is a VGAM511 host target gene. CDH6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDH6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2



illustrates the complementarity of the nucleotide sequences of CDH6 BINDING SITE, designated SEQ ID:11372, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23015] A function of VGAM511 is therefore inhibition of Cadherin 6, Type 2, K-cadherin (fetal kidney) (CDH6, Accession NM\_004932), a gene which is a calcium dependent cell adhesion protein. Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH6. The function of CDH6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM60. Interferon Regulatory Factor 2 (IRF2, Accession NM\_002199) is another VGAM511 host target gene. IRF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IRF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IRF2 BINDING SITE, designated SEQ ID:7957, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23016] Another function of VGAM511 is therefore inhibition of Interferon Regulatory Factor 2 (IRF2, Accession NM\_002199), a gene which is a transcriptional activator of type I interferon and interferon-inducible genes. Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IRF2. The function of IRF2 has been established by previous studies. Interferon regulatory factor-1 (IRF1; 147575), a transcriptional activator, and IRF2, its antagonistic repressor, are regulators of type I interferon and interferon-inducible genes. The IRF1 gene is itself interferon-inducible and hence may be one of the target genes critical for interferon action. Harada et al. (1993) found that when the IRF2 gene was overexpressed in NIH 3T3 cells, the cells became transformed and displayed enhanced tumorigenicity in nude mice. This transformed phenotype was reversed by concomitant expression of the IRF1 gene. Thus, restrained cell growth depends on a balance between these 2 mutually antagonistic transcription factors Nishio et al. (2001) screened for mutations in the 5-prime flanking and coding regions of IRF2 in patients with atopic dermatitis (see OMIM Ref. No. 603165). They found 5 novel variants and conducted a transmission dis-

equilibrium test in families identified through patients with atopic dermatitis. The data suggested that the IRF2 gene may play a role in the development of atopic dermatitis in Japanese Ko et al. (2002) noted that *Irf1*  $-/-$  mice are deficient in *Inos* (OMIM Ref. No. 163730), *Il12b* (OMIM Ref. No. 161561), Cd8-positive T cells, and natural killer (NK) cells, whereas *Irf2*  $-/-$  mice are deficient in NK cells and have dysregulated *Il12b* induction. *Icsbp* (OMIM Ref. No. 601565)  $-/-$  mice are deficient in *Il12b*, *Irf2*, and reactive oxygen intermediates (ROIs). All 3 are inducible by gamma-interferon (*Ifng*; 147570) and have varying susceptibility to different intracellular bacterial and protozoan pathogens. Ko et al. (2002) determined that *Irf1*  $-/-$  mice are highly susceptible to fatal liver damage from *Brucella abortus*, the causative agent of brucellosis, which manifests as arthritis, endocarditis, and meningitis in humans. In contrast, *Irf2*  $-/-$  mice are highly resistant to *Brucella*, whereas *Icsbp*  $-/-$  mice maintain a plateau of infection similar to that seen in *Il12b*  $-/-$  mice. The authors concluded that IL12, reactive nitrogen intermediates, and ROIs are probably crucial immune components in resistance to *Brucella* infection. Animal model experiments lend further support to the function of IRF2. Hida et al. (2000)

observed that *Irf2*  $-/-$  mice exhibited progressive cutaneous inflammation accompanied by hair loss and ulcer formation. Histopathologic analysis demonstrated epidermal thickening with proliferating keratinocytes expressing *Icam1*/Cd54 (OMIM Ref. No. 147840), features similar to those found in psoriasis. In addition, however, there was a disorganized muscle layer and prominent fibrosis. In the basal dermis, infiltrating Cd8 (see OMIM Ref. No. 186910)-positive rather than Cd4 (OMIM Ref. No. 186940)-positive T cells were involved in the development of disease. In vitro analysis showed that the Cd8 T cells exhibited prolonged activation and proliferation with high expression of Cd44 (OMIM Ref. No. 107269) and Ly6c. RT-PCR and Northern blot analysis detected spontaneous expression of *Ifna* (OMIM Ref. No. 147660) and *Ifnb* (OMIM Ref. No. 147640), as well as overexpression of IFN-inducible genes, i.e., *Oas* (see OMIM Ref. No. 603351), *Irf7* (OMIM Ref. No. 605047), *Ip10* (SCYB10; 147310), and *Mig* (SCYB9; 601704), in the *Irf2*  $-/-$  mice. Inactivation of the *Ifna*/*Ifnb* pathways by mutating *Ifnar1* (OMIM Ref. No. 107450) or *Irf9* resulted in the absence of skin disease in *Irf2*  $-/-$  mice.

[23017] It is appreciated that the abovementioned animal model

for IRF2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[23018] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23019] Ko, J.; Gendron-Fitzpatrick, A.; Splitter, G. A. : Susceptibility of IFN regulatory factor-1 and IFN consensus sequence binding protein-deficient mice to brucellosis. J. Immun. 168: 2433-2440, 2002. ; and

[23020] Nishio, Y.; Noguchi, E.; Ito, S.; Ichikawa, E.; Umebayashi, Y.; Otsuka, F.; Arinami, T. : Mutation and association analysis of the interferon regulatory factor 2 gene (IRF2) with atopic.

[23021] Further studies establishing the function and utilities of IRF2 are found in John Hopkins OMIM database record ID 147576, and in cited publications numbered 3397-3399, 339 and 3400 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Sal-like 1 (Drosophila) (SALL1, Accession NM\_002968) is another VGAM511 host target gene. SALL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SALL1, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SALL1 BINDING SITE, designated SEQ ID:8879, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23022] Another function of VGAM511 is therefore inhibition of Sal-like 1 (Drosophila) (SALL1, Accession NM\_002968). Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SALL1. DKFZP547L112 (Accession XM\_039353) is another VGAM511 host target gene. DKFZP547L112 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZP547L112, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP547L112 BINDING SITE, designated SEQ ID:33056, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23023] Another function of VGAM511 is therefore inhibition of DKFZP547L112 (Accession XM\_039353). Accordingly, util-

ities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP547L112. Tripartite Motif-containing 2 (TRIM2, Accession NM\_015271) is another VGAM511 host target gene. TRIM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM2 BINDING SITE, designated SEQ ID:17596, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23024] Another function of VGAM511 is therefore inhibition of Tripartite Motif-containing 2 (TRIM2, Accession NM\_015271). Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM2. LOC161403 (Accession XM\_090873) is another VGAM511 host target gene. LOC161403 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC161403, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161403 BINDING SITE, designated SEQ ID:40019, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23025] Another function of VGAM511 is therefore inhibition of LOC161403 (Accession XM\_090873). Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161403. LOC199926 (Accession XM\_117157) is another VGAM511 host target gene. LOC199926 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199926, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199926 BINDING SITE, designated SEQ ID:43261, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23026] Another function of VGAM511 is therefore inhibition of LOC199926 (Accession XM\_117157). Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC199926. LOC202316 (Accession XM\_117380) is another VGAM511 host target gene. LOC202316 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202316 BINDING SITE, designated SEQ ID:43426, to the nucleotide sequence of VGAM511 RNA, herein designated VGAM RNA, also designated SEQ ID:3222.

[23027] Another function of VGAM511 is therefore inhibition of LOC202316 (Accession XM\_117380). Accordingly, utilities of VGAM511 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202316. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 512 (VGAM512) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23028] VGAM512 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM512 was detected is described hereinabove with reference to Figs. 1–8.

[23029] VGAM512 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cucumber Green Mottle Mosaic Virus. VGAM512 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23030] VGAM512 gene encodes a VGAM512 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM512 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM512 precursor RNA is designated SEQ ID:498, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:498 is located at position 2385 relative to the genome of Cucumber Green Mottle Mosaic Virus.

[23031] VGAM512 precursor RNA folds onto itself, forming VGAM512 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23032] An enzyme complex designated DICER COMPLEX, `dices` the VGAM512 folded precursor RNA into VGAM512 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 86%) nucleotide sequence of VGAM512 RNA is designated SEQ ID:3223, and is provided hereinbelow with reference to the sequence listing part.

[23033] VGAM512 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM512 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM512 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23034] VGAM512 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM512 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM512 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM512 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM512 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23035] The complementary binding of VGAM512 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM512 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM512 host target RNA into VGAM512 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23036] It is appreciated that VGAM512 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM512 host target genes. The mRNA of each one of this plurality of VGAM512 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM512 RNA, herein designated VGAM RNA, and which when bound by VGAM512 RNA causes inhibition of translation of respective one or more VGAM512 host target proteins.

[23037] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM512 gene, herein designated VGAM GENE, on one or more VGAM512 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23038] It is yet further appreciated that a function of VGAM512 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM512 include diagnosis, prevention and treatment of viral infection by Cucumber Green Mottle Mosaic Virus. Specific functions, and accordingly utilities, of VGAM512 correlate with, and may be deduced from, the identity of the host target genes which VGAM512 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23039] Nucleotide sequences of the VGAM512 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM512 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM512 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM512 are further described hereinbelow with reference to Table 1.

[23040] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM512 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM512 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23041] As mentioned hereinabove with reference to Fig. 1, a function of VGAM512 gene, herein designated VGAM is inhibition of expression of VGAM512 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM512 correlate with, and may be deduced from, the identity of the target genes which VGAM512 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23042] RAB1A, Member RAS Oncogene Family (RAB1A, Accession XM\_046674) is a VGAM512 host target gene. RAB1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB1A, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB1A BINDING SITE, designated SEQ ID:34787, to the nucleotide sequence of VGAM512 RNA, herein designated VGAM RNA, also designated SEQ ID:3223.

[23043] A function of VGAM512 is therefore inhibition of RAB1A, Member RAS Oncogene Family (RAB1A, Accession XM\_046674), a gene which is involved in vesicle transport. Accordingly, utilities of VGAM512 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB1A. The function of RAB1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM433. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 513 (VGAM513) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23044] VGAM513 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The



method by which VGAM513 was detected is described hereinabove with reference to Figs. 1–8.

[23045] VGAM513 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cucumber Green Mottle Mosaic Virus. VGAM513 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23046] VGAM513 gene encodes a VGAM513 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM513 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM513 precursor RNA is designated SEQ ID:499, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:499 is located at position 2231 relative to the genome of Cucumber Green Mottle Mosaic Virus.

[23047] VGAM513 precursor RNA folds onto itself, forming VGAM513 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23048] An enzyme complex designated DICER COMPLEX, `dices` the VGAM513 folded precursor RNA into VGAM513 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM513 RNA is designated SEQ ID:3224, and is provided hereinbelow with reference to the sequence listing part.

[23049] VGAM513 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM513 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM513 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23050] VGAM513 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM513 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM513 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM513 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM513 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23051] The complementary binding of VGAM513 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM513 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM513 host target RNA into VGAM513 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23052] It is appreciated that VGAM513 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM513 host target genes. The mRNA of each one of this plurality of VGAM513 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM513 RNA, herein designated VGAM RNA, and which when bound by VGAM513 RNA causes inhibition of translation of respective one or more VGAM513 host target proteins.

[23053] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM513 gene, herein designated VGAM GENE, on one or more VGAM513 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23054] It is yet further appreciated that a function of VGAM513 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM513 include diagnosis, prevention and treatment of viral infection by Cucumber Green Mottle Mosaic Virus. Specific functions, and accordingly utilities, of VGAM513 correlate with, and may be deduced from, the identity of the host target genes which VGAM513 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23055] Nucleotide sequences of the VGAM513 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM513 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM513 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM513 are further described hereinbelow with reference to Table 1.

[23056] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM513 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM513 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23057] As mentioned hereinabove with reference to Fig. 1, a function of VGAM513 gene, herein designated VGAM is inhibition of expression of VGAM513 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM513 correlate with, and may be deduced from, the identity of the target genes which VGAM513 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23058] LAG1 Longevity Assurance Homolog 2 (*S. cerevisiae*) (LASS2, Accession XM\_041889) is a VGAM513 host target gene. LASS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

LASS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LASS2 BINDING SITE, designated SEQ ID:33623, to the nucleotide sequence of VGAM513 RNA, herein designated VGAM RNA, also designated SEQ ID:3224.

[23059] A function of VGAM513 is therefore inhibition of LAG1 Longevity Assurance Homolog 2 (*S. cerevisiae*) (LASS2, Accession XM\_041889). Accordingly, utilities of VGAM513 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LASS2. FLJ14249 (Accession NM\_022460) is another VGAM513 host target gene. FLJ14249 BINDING SITE1 and FLJ14249 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ14249, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14249 BINDING SITE1 and FLJ14249 BINDING SITE2, designated SEQ ID:22798 and SEQ ID:28168 respectively, to the nucleotide sequence of VGAM513 RNA, herein designated VGAM RNA, also designated SEQ ID:3224.

[23060] Another function of VGAM513 is therefore inhibition of FLJ14249 (Accession NM\_022460). Accordingly, utilities of VGAM513 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14249. LOC149103 (Accession XM\_086434) is another VGAM513 host target gene. LOC149103 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149103 BINDING SITE, designated SEQ ID:38652, to the nucleotide sequence of VGAM513 RNA, herein designated VGAM RNA, also designated SEQ ID:3224.

[23061] Another function of VGAM513 is therefore inhibition of LOC149103 (Accession XM\_086434). Accordingly, utilities of VGAM513 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149103. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 514 (VGAM514) viral gene, which modulates expression of respective host target genes thereof,



the function and utility of which host target genes is known in the art.

[23062] VGAM514 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM514 was detected is described hereinabove with reference to Figs. 1–8.

[23063] VGAM514 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cucumber Green Mottle Mosaic Virus. VGAM514 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23064] VGAM514 gene encodes a VGAM514 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM514 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM514 precursor RNA is designated SEQ ID:500, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:500 is located at position 1818 relative to the genome of Cucumber Green Mottle Mosaic Virus.

[23065] VGAM514 precursor RNA folds onto itself, forming VGAM514 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[23066] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM514 folded precursor RNA into VGAM514 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 80%) nucleotide se-  
quence of VGAM514 RNA is designated SEQ ID:3225, and  
is provided hereinbelow with reference to the sequence  
listing part.

[23067] VGAM514 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM514 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM514 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23068] VGAM514 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM514 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM514 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM514 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM514 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23069] The complementary binding of VGAM514 RNA, herein designated VGAM RNA, to host target binding sites on VGAM514 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM514 host target RNA into VGAM514 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23070] It is appreciated that VGAM514 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM514 host target genes. The mRNA of each one of this plurality of VGAM514 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM514 RNA, herein designated VGAM RNA, and which when bound by VGAM514 RNA causes inhibition of translation of respective one or more VGAM514 host target proteins.

[23071] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM514 gene, herein designated VGAM GENE, on one or more VGAM514 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23072] It is yet further appreciated that a function of VGAM514 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of viral infection by Cucumber Green Mottle Mosaic Virus. Specific functions, and accordingly utilities, of VGAM514 correlate with, and may be deduced from, the identity of the host target genes which VGAM514 binds and inhibits, and the function of these host target

genes, as elaborated hereinbelow.

[23073] Nucleotide sequences of the VGAM514 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM514 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM514 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM514 are further described hereinbelow with reference to Table 1.

[23074] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM514 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM514 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23075] As mentioned hereinabove with reference to Fig. 1, a function of VGAM514 gene, herein designated VGAM is inhibition of expression of VGAM514 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM514 correlate with, and may be deduced from, the identity of the target genes which VGAM514 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23076] Galanin (GAL, Accession XM\_166189) is a VGAM514 host target gene. GAL BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GAL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAL BINDING SITE, designated SEQ ID:43998, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23077] A function of VGAM514 is therefore inhibition of Galanin (GAL, Accession XM\_166189), a gene which stimulates LH secretion and enhances LHRH-induced LH release from dispersed anterior pituitary cells in vitro. Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAL. The function of GAL has been established by previous studies. Galanin is a 29-amino acid peptide widely distributed in the peripheral and central nervous systems. In the brain, the highest concentrations are observed in the hypothalamus and particularly in the nerve terminals of the median eminence. Since the establishment of the neurovascular concept in the regulation of the

hypothalamus–pituitary axis (Harris, 1948), it is well known that the median eminence represents a key area for neuroendocrine regulation. Hypothalamic releasing and inhibiting factors are secreted from median eminence terminals into the portal circulation to reach the adenohypophyseal cells where they exert specific actions. Lopez et al. (1991) presented evidence that galanin meets the criteria to be considered a hypothalamic–hypophysiotropic hormone. They found a possibly meaningful colocalization and cosecretion of galanin and LHRH (OMIM Ref. No. 152760). Galanin stimulates LH secretion and enhances LHRH–induced LH release from dispersed anterior pituitary cells in vitro. Galanin is important to gastrointestinal function also (Rattan, 1991). Animal model experiments lend further support to the function of GAL. The neuropeptide galanin is predominantly expressed by the lactotrophs (the prolactin–secreting cell type) in the rodent anterior pituitary and in the median eminence and paraventricular nucleus of the hypothalamus. Prolactin (PRL; 176760) and galanin colocalize in the same secretory granule, and the expression of both proteins is extremely sensitive to the estrogen status of the animal. Administration of estradiol–17–beta induces pituitary hyperplasia



followed by adenoma formation and causes a 3,000-fold increase in the galanin mRNA content of the lactotroph. To further study the role of galanin in prolactin release and lactotroph growth, Wynick et al. (1998) generated mice carrying a loss-of-function mutation of the endogenous galanin gene. There was no evidence of embryonic lethality and the mutant mice grew normally. The specific endocrine abnormalities identified related to the expression of prolactin. Pituitary prolactin message levels and protein content of adult female mutant mice were reduced by 30 to 40% compared with wildtype controls. Mutant females failed to lactate and pups died of starvation/dehydration unless fostered onto wildtype mothers. Prolactin secretion in mutant females was markedly reduced at 7 days postpartum compared with wildtype controls with an associated failure in mammary gland maturation. There was almost complete abrogation of the proliferative response of the lactotroph to high doses of estrogen, with a failure to upregulate prolactin release and STAT5 (OMIM Ref. No. 601511) expression or to increase pituitary cell number. These data supported the hypothesis that galanin acts as a paracrine regulator of prolactin expression and as a growth factor to the lactotroph.

- [23078] It is appreciated that the abovementioned animal model for GAL is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.
- [23079] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [23080] Wynick, D.; Small, C. J.; Bacon, A.; Holmes, F. E.; Norman, M.; Ormandy, C. J.; Kilic, E.; Kerr, N. C. H.; Ghatei, M.; Talamantes, F.; Bloom, S. R.; Pachnis, V. : Galanin regulates prolactin release and lactotroph proliferation. *Proc. Nat. Acad. Sci.* 95: 12671–12676, 1998. ; and
- [23081] Lopez, F. J.; Merchenthaler, I.; Ching, M.; Wisniewski, M. G.; Negro-Vilar, A. : Galanin: a hypothalamic-hypophysiotropic hormone modulating reproductive functions. *Proc. Nat. Acad. Sci.*
- [23082] Further studies establishing the function and utilities of GAL are found in John Hopkins OMIM database record ID 137035, and in sited publications numbered 4054–4065 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Potassium Channel, Subfamily K, Member 4 (KCNK4, Accession NM\_016611) is another VGAM514 host target gene. KCN4 BINDING SITE

is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KCNK4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNK4 BINDING SITE, designated SEQ ID:18714, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23083] Another function of VGAM514 is therefore inhibition of Potassium Channel, Subfamily K, Member 4 (KCNK4, Accession NM\_016611). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNK4. LIM Domain Kinase 1 (LIMK1, Accession NM\_016735) is another VGAM514 host target gene. LIMK1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LIMK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LIMK1 BINDING SITE, designated SEQ ID:18798, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23084] Another function of VGAM514 is therefore inhibition of LIM Domain Kinase 1 (LIMK1, Accession NM\_016735). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LIMK1. Matrix Metalloproteinase 25 (MMP25, Accession NM\_022468) is another VGAM514 host target gene. MMP25 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MMP25, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MMP25 BINDING SITE, designated SEQ ID:22821, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23085] Another function of VGAM514 is therefore inhibition of Matrix Metalloproteinase 25 (MMP25, Accession NM\_022468). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MMP25. MLL Septin-like Fusion (MSF, Accession XM\_113892) is another VGAM514 host target gene. MSF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by MSF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSF BINDING SITE, designated SEQ ID:42521, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23086] Another function of VGAM514 is therefore inhibition of MLL Septin-like Fusion (MSF, Accession XM\_113892), a gene which plays a role in the cell cycle. Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSF. The function of MSF has been established by previous studies. Bahabri et al. (1998) mapped the locus for autosomal recessive camptodactyly–arthropathy–coxa vara–pericarditis syndrome (CACP; 208250) to chromosome 1q25–q31. Marcelino et al. (1999) independently identified the CACP gene using a positional cloning approach. They determined that the MSF and CACP genes are the same. Analysis of a human multitissue Northern blot demonstrated that the 4.5–kb CACP mRNA is expressed in tissues including liver, lung, and heart. It is highly expressed in synovial tissue. The 30–kD N-terminal

megakaryocyte–stimulating factor fragment was detectable in serum and urine. Marcelino et al. (1999) identified 8 likely disease–causing mutations in patients with CACP from consanguineous families. Four were homozygous deletions. Additionally, they detected a dinucleotide transversion that created a nonsense codon, and a 41–bp insertion 14 nucleotides upstream of the intron 6 splice acceptor site that disrupted the polypyrimidine tract of the splice site. Each of these mutations was predicted to result in a truncated protein. Due to its high glycosylation content and mucin–like repeats, Marcelino et al. (1999) suggested that CACP may act as a joint/intimal cell lubricant. Both synovial and pericardial cell hyperplasia may represent secondary consequences of insufficient cell surface lubrication. Alternatively, cell overgrowth may be primary to the pathogenesis of CACP. The occurrence of multiple small ganglion cysts in 2 unrelated patients, and of coxa vara deformity in this disorder, suggested a regulatory role for the CACP protein product to Marcelino et al. (1999).

[23087] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [23088] Bahabri, S. A.; Suwairi, W. M.; Laxer, R. M.; Polinkovsky, A.; Dalaan, A. A.; Warman, M. L. : The camptodactyly–arthropathy–coxa vara–pericarditis syndrome: clinical features and genetic mapping to human chromosome 1. *Arthritis Rheum.* 41: 730–735, 1998. ; and
- [23089] Marcelino, J.; Carpten, J. D.; Suwairi, W. M.; Gutierrez, O. M.; Schwartz, S.; Robbins, C.; Sood, R.; Makalowska, I.; Baxevanis, A.; Johnstone, B.; Laxer, R. M.; Zemel, L.; and 13 other.
- [23090] Further studies establishing the function and utilities of MSF are found in John Hopkins OMIM database record ID 604283, and in cited publications numbered 2073, 7617–7618, 207 and 7619–7620 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. PTK7 Protein Tyrosine Kinase 7 (PTK7, Accession NM\_002821) is another VGAM514 host target gene. PTK7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTK7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTK7 BINDING SITE, designated SEQ ID:8688, to the nucleotide sequence of VGAM514 RNA, herein des–

ignated VGAM RNA, also designated SEQ ID:3225.

[23091] Another function of VGAM514 is therefore inhibition of PTK7 Protein Tyrosine Kinase 7 (PTK7, Accession NM\_002821), a gene which is a glycosylated receptor protein tyrosine kinase and may function as a cell adhesion molecule. Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTK7. The function of PTK7 has been established by previous studies. Protein-tyrosine kinases (PTKs) play important roles in regulating cell proliferation and differentiation during development. Lee et al. (1993) isolated a 220-bp fragment of PTK7 cDNA through a screen designed to identify tyrosine kinase mRNAs expressed in normal human melanocytes. This fragment was mapped to chromosome 6 by Southern blotting using a panel of human-hamster somatic cell hybrids. Park et al. (1996) isolated a full-length PTK7 cDNA and found that it encodes a receptor protein-tyrosine kinase-like molecule closely related to a chick kinase-like gene whose function was unknown. Mossie et al. (1995) independently isolated the PTK7 gene from colon carcinoma and designated it colon carcinoma kinase-4. Banga et al. (1997) sublocalized the PTK7 gene to 6p21.1-p12.2 by fluorescence in



situ hybridization.

[23092] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23093] Lee, S.-T.; Strunk, K. M.; Spritz, R. A. : A survey of protein tyrosine kinase mRNAs expressed in normal human melanocytes. *Oncogene* 8: 3403–3410, 1993. ; and

[23094] Park, S.-K.; Lee, H.-S.; Lee, S.-T. : Characterization of the human full-length PTK7 cDNA encoding a receptor protein tyrosine kinase-like molecule closely related to chick KLG. *J. Bioch.*

[23095] Further studies establishing the function and utilities of PTK7 are found in John Hopkins OMIM database record ID 601890, and in cited publications numbered 6703–6706 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ring Finger Protein 4 (RNF4, Accession NM\_002938) is another VGAM514 host target gene. RNF4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF4 BINDING SITE, designated

SEQ ID:8840, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23096] Another function of VGAM514 is therefore inhibition of Ring Finger Protein 4 (RNF4, Accession NM\_002938). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNF4. Solute Carrier Family 8 (sodium-calcium exchanger), Member 2 (SLC8A2, Accession XM\_038970) is another VGAM514 host target gene. SLC8A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC8A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC8A2 BINDING SITE, designated SEQ ID:32967, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23097] Another function of VGAM514 is therefore inhibition of Solute Carrier Family 8 (sodium-calcium exchanger), Member 2 (SLC8A2, Accession XM\_038970). Accordingly, utilities of VGAM514 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with SLC8A2. DKFZP727G051 (Accession XM\_045308) is another VGAM514 host target gene. DKFZP727G051 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP727G051, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP727G051 BINDING SITE, designated SEQ ID:34429, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23098] Another function of VGAM514 is therefore inhibition of DKFZP727G051 (Accession XM\_045308). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP727G051. FLJ00007 (Accession XM\_048928) is another VGAM514 host target gene. FLJ00007 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ00007, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

FLJ00007 BINDING SITE, designated SEQ ID:35308, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23099] Another function of VGAM514 is therefore inhibition of FLJ00007 (Accession XM\_048928). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00007. KIAA0237 (Accession NM\_014747) is another VGAM514 host target gene. KIAA0237 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0237 BINDING SITE, designated SEQ ID:16444, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23100] Another function of VGAM514 is therefore inhibition of KIAA0237 (Accession NM\_014747). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0237. KIAA1656 (Accession XM\_038022) is another VGAM514 host target gene. KIAA1656 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1656, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1656 BINDING SITE, designated SEQ ID:32728, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23101] Another function of VGAM514 is therefore inhibition of KIAA1656 (Accession XM\_038022). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1656. LOC112840 (Accession NM\_080666) is another VGAM514 host target gene. LOC112840 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC112840, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112840 BINDING SITE, designated SEQ ID:27956, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23102] Another function of VGAM514 is therefore inhibition of

LOC112840 (Accession NM\_080666). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112840. LOC115207 (Accession NM\_138444) is another VGAM514 host target gene. LOC115207 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115207, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115207 BINDING SITE, designated SEQ ID:28807, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23103] Another function of VGAM514 is therefore inhibition of LOC115207 (Accession NM\_138444). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115207. LOC147136 (Accession XM\_085716) is another VGAM514 host target gene. LOC147136 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147136, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC147136 BINDING SITE, designated SEQ ID:38300, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23104] Another function of VGAM514 is therefore inhibition of LOC147136 (Accession XM\_085716). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147136. LOC222031 (Accession XM\_168371) is another VGAM514 host target gene. LOC222031 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222031, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222031 BINDING SITE, designated SEQ ID:45131, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23105] Another function of VGAM514 is therefore inhibition of LOC222031 (Accession XM\_168371). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222031. LOC254556 (Accession XM\_170588) is an-

other VGAM514 host target gene. LOC254556 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254556 BINDING SITE, designated SEQ ID:45393, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23106] Another function of VGAM514 is therefore inhibition of LOC254556 (Accession XM\_170588). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254556. LOC257428 (Accession XM\_168584) is another VGAM514 host target gene. LOC257428 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257428 BINDING SITE, designated SEQ ID:45261, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.



[23107] Another function of VGAM514 is therefore inhibition of LOC257428 (Accession XM\_168584). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257428. LOC56965 (Accession NM\_020213) is another VGAM514 host target gene. LOC56965 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC56965, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC56965 BINDING SITE, designated SEQ ID:21451, to the nucleotide sequence of VGAM514 RNA, herein designated VGAM RNA, also designated SEQ ID:3225.

[23108] Another function of VGAM514 is therefore inhibition of LOC56965 (Accession NM\_020213). Accordingly, utilities of VGAM514 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC56965. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 515 (VGAM515) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[23109] VGAM515 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM515 was detected is described hereinabove with reference to Figs. 1–8.

[23110] VGAM515 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cucumber Green Mottle Mosaic Virus. VGAM515 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23111] VGAM515 gene encodes a VGAM515 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM515 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM515 precursor RNA is designated SEQ ID:501, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:501 is located at position 4400 relative to the genome of Cucumber Green Mottle Mosaic Virus.

[23112] VGAM515 precursor RNA folds onto itself, forming VGAM515 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[23113] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM515 folded precursor RNA into VGAM515 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM515 RNA is designated SEQ ID:3226, and  
is provided hereinbelow with reference to the sequence  
listing part.

[23114] VGAM515 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM515 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM515 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23115] VGAM515 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM515 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM515 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM515 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM515 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23116] The complementary binding of VGAM515 RNA, herein designated VGAM RNA, to host target binding sites on VGAM515 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM515 host target RNA into VGAM515 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23117] It is appreciated that VGAM515 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM515 host target genes. The mRNA of each one of this plurality of VGAM515 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM515 RNA, herein designated VGAM RNA, and which when bound by VGAM515 RNA causes inhibition of translation of respective one or more VGAM515 host target proteins.

[23118] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM515 gene, herein designated VGAM GENE, on one or more VGAM515 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23119] It is yet further appreciated that a function of VGAM515 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of viral infection by Cucumber Green Mottle Mosaic Virus. Specific functions, and accordingly utilities, of VGAM515 correlate with, and may be deduced from, the identity of the host target genes which VGAM515 binds and inhibits, and the function of these host target

genes, as elaborated hereinbelow.

- [23120] Nucleotide sequences of the VGAM515 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM515 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM515 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM515 are further described hereinbelow with reference to Table 1.
- [23121] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM515 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM515 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [23122] As mentioned hereinabove with reference to Fig. 1, a function of VGAM515 gene, herein designated VGAM is inhibition of expression of VGAM515 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM515 correlate with, and may be deduced from, the identity of the target genes which VGAM515 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23123] B-cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898) is a VGAM515 host target gene. BCL11B BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by BCL11B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL11B BINDING SITE, designated SEQ ID:23162, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23124] A function of VGAM515 is therefore inhibition of B-cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL11B. Homeo Box A7 (HOXA7, Accession NM\_006896) is another VGAM515 host target gene. HOXA7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HOXA7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HOXA7 BINDING SITE, designated



SEQ ID:13771, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23125] Another function of VGAM515 is therefore inhibition of Homeo Box A7 (HOXA7, Accession NM\_006896), a gene which provides cells with specific positional identities on the anterior-posterior axis. Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HOXA7. The function of HOXA7 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM206.DKFZP566G1424 (Accession XM\_097771) is another VGAM515 host target gene. DKFZP566G1424 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP566G1424, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566G1424 BINDING SITE, designated SEQ ID:41114, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23126] Another function of VGAM515 is therefore inhibition of DKFZP566G1424 (Accession XM\_097771). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566G1424. FLJ11125 (Accession XM\_005318) is another VGAM515 host target gene. FLJ11125 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11125, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11125 BINDING SITE, designated SEQ ID:29977, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23127] Another function of VGAM515 is therefore inhibition of FLJ11125 (Accession XM\_005318). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11125. KIAA1465 (Accession XM\_027396) is another VGAM515 host target gene. KIAA1465 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1465 BINDING SITE, designated SEQ ID:30506, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23128] Another function of VGAM515 is therefore inhibition of KIAA1465 (Accession XM\_027396). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1465. KIAA1771 (Accession XM\_086404) is another VGAM515 host target gene. KIAA1771 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1771, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1771 BINDING SITE, designated SEQ ID:38635, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23129] Another function of VGAM515 is therefore inhibition of KIAA1771 (Accession XM\_086404). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1771. Nuclear Factor of Activated T-cells 5, Tonicity-responsive (NFAT5, Accession NM\_138714) is another VGAM515 host target gene. NFAT5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NFAT5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFAT5 BINDING SITE, designated SEQ ID:28959, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23130] Another function of VGAM515 is therefore inhibition of Nuclear Factor of Activated T-cells 5, Tonicity-responsive (NFAT5, Accession NM\_138714). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NFAT5. Protocadherin 17 (PCDH17, Accession NM\_014459) is another VGAM515 host target gene. PCDH17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDH17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDH17

BINDING SITE, designated SEQ ID:15814, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23131] Another function of VGAM515 is therefore inhibition of Protocadherin 17 (PCDH17, Accession NM\_014459). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH17. SSB-3 (Accession NM\_080861) is another VGAM515 host target gene. SSB-3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SSB-3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSB-3 BINDING SITE, designated SEQ ID:28101, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23132] Another function of VGAM515 is therefore inhibition of SSB-3 (Accession NM\_080861). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSB-3. LOC152300 (Accession XM\_087432) is another VGAM515 host target gene. LOC152300 BINDING SITE is HOST TAR-

GET binding site found in the 3' untranslated region of mRNA encoded by LOC152300, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152300 BINDING SITE, designated SEQ ID:39250, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23133] Another function of VGAM515 is therefore inhibition of LOC152300 (Accession XM\_087432). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152300. LOC207089 (Accession XM\_115923) is another VGAM515 host target gene. LOC207089 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC207089, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC207089 BINDING SITE, designated SEQ ID:43108, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23134] Another function of VGAM515 is therefore inhibition of

LOC207089 (Accession XM\_115923). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC207089. LOC221399 (Accession XM\_168134) is another VGAM515 host target gene. LOC221399 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221399, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221399 BINDING SITE, designated SEQ ID:45049, to the nucleotide sequence of VGAM515 RNA, herein designated VGAM RNA, also designated SEQ ID:3226.

[23135] Another function of VGAM515 is therefore inhibition of LOC221399 (Accession XM\_168134). Accordingly, utilities of VGAM515 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221399. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 516 (VGAM516) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[23136] VGAM516 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM516 was detected is described hereinabove with reference to Figs. 1–8.

[23137] VGAM516 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Galinsoga Mosaic Virus. VGAM516 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23138] VGAM516 gene encodes a VGAM516 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM516 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM516 precursor RNA is designated SEQ ID:502, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:502 is located at position 2863 relative to the genome of Galinsoga Mosaic Virus.

[23139] VGAM516 precursor RNA folds onto itself, forming VGAM516 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional



`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[23140] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM516 folded precursor RNA into VGAM516 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 79%) nucleotide se-  
quence of VGAM516 RNA is designated SEQ ID:3227, and  
is provided hereinbelow with reference to the sequence  
listing part.

[23141] VGAM516 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM516 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM516 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[23142] VGAM516 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM516 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM516 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM516 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM516 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[23143] The complementary binding of VGAM516 RNA, herein designated VGAM RNA, to host target binding sites on VGAM516 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM516 host target RNA into VGAM516 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23144] It is appreciated that VGAM516 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM516 host target genes. The mRNA of each one of this plurality of VGAM516 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM516 RNA, herein designated VGAM RNA, and which when bound by VGAM516 RNA causes inhibition of translation of respective one or more VGAM516 host target proteins.

[23145] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM516 gene, herein designated VGAM GENE, on one or

more VGAM516 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23146] It is yet further appreciated that a function of VGAM516 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of viral infection by Galinsoga Mosaic Virus. Specific functions, and accordingly utilities, of VGAM516 correlate with, and may be deduced from, the identity of the host target genes which VGAM516 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [23147] Nucleotide sequences of the VGAM516 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM516 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM516 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM516 are further described hereinbelow with reference to Table 1.
- [23148] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM516 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM516 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [23149] As mentioned hereinabove with reference to Fig. 1, a function of VGAM516 gene, herein designated VGAM is inhibition of expression of VGAM516 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM516 correlate with, and may be deduced from, the identity of the target genes which VGAM516 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [23150] Bromodomain Adjacent to Zinc Finger Domain, 1B (BAZ1B,

Accession NM\_032408) is a VGAM516 host target gene. BAZ1B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BAZ1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BAZ1B BINDING SITE, designated SEQ ID:26192, to the nucleotide sequence of VGAM516 RNA, herein designated VGAM RNA, also designated SEQ ID:3227.

[23151] A function of VGAM516 is therefore inhibition of Bromodomain Adjacent to Zinc Finger Domain, 1B (BAZ1B, Accession NM\_032408). Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BAZ1B. APCL (Accession NM\_005883) is another VGAM516 host target gene. APCL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APCL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APCL BINDING SITE, designated SEQ ID:12495, to the nucleotide sequence of VGAM516 RNA, herein designated

VGAM RNA, also designated SEQ ID:3227.

[23152] Another function of VGAM516 is therefore inhibition of APCL (Accession NM\_005883). Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APCL. FLJ14547 (Accession NM\_032804) is another VGAM516 host target gene. FLJ14547 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14547, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14547 BINDING SITE, designated SEQ ID:26559, to the nucleotide sequence of VGAM516 RNA, herein designated VGAM RNA, also designated SEQ ID:3227.

[23153] Another function of VGAM516 is therefore inhibition of FLJ14547 (Accession NM\_032804). Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14547. PRAX-1 (Accession NM\_004758) is another VGAM516 host target gene. PRAX-1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PRAX-1, corresponding to a HOST TARGET bind-

ing site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRAX-1 BINDING SITE, designated SEQ ID:11145, to the nucleotide sequence of VGAM516 RNA, herein designated VGAM RNA, also designated SEQ ID:3227.

[23154] Another function of VGAM516 is therefore inhibition of PRAX-1 (Accession NM\_004758). Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRAX-1. Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654) is another VGAM516 host target gene. SDC3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SDC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDC3 BINDING SITE, designated SEQ ID:16086, to the nucleotide sequence of VGAM516 RNA, herein designated VGAM RNA, also designated SEQ ID:3227.

[23155] Another function of VGAM516 is therefore inhibition of Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654). Accordingly, utilities of VGAM516 include diagnosis, pre-



vention and treatment of diseases and clinical conditions associated with SDC3. LOC150577 (Accession XM\_097918) is another VGAM516 host target gene. LOC150577 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC150577, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150577 BINDING SITE, designated SEQ ID:41224, to the nucleotide sequence of VGAM516 RNA, herein designated VGAM RNA, also designated SEQ ID:3227.

[23156] Another function of VGAM516 is therefore inhibition of LOC150577 (Accession XM\_097918). Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150577. LOC151162 (Accession XM\_098012) is another VGAM516 host target gene. LOC151162 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC151162, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC151162 BINDING SITE, designated SEQ ID:41307, to the nucleotide sequence of VGAM516 RNA, herein designated VGAM RNA, also designated SEQ ID:3227.

[23157] Another function of VGAM516 is therefore inhibition of LOC151162 (Accession XM\_098012). Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151162. LOC203377 (Accession XM\_117540) is another VGAM516 host target gene. LOC203377 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC203377, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203377 BINDING SITE, designated SEQ ID:43542, to the nucleotide sequence of VGAM516 RNA, herein designated VGAM RNA, also designated SEQ ID:3227.

[23158] Another function of VGAM516 is therefore inhibition of LOC203377 (Accession XM\_117540). Accordingly, utilities of VGAM516 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203377. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 517 (VGAM517) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23159] VGAM517 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM517 was detected is described hereinabove with reference to Figs. 1–8.

[23160] VGAM517 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Galinsoga Mosaic Virus. VGAM517 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23161] VGAM517 gene encodes a VGAM517 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM517 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM517 precursor RNA is designated SEQ ID:503, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:503 is located at position 3248 relative to the genome of Galin–

soga Mosaic Virus.

[23162] VGAM517 precursor RNA folds onto itself, forming VGAM517 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23163] An enzyme complex designated DICER COMPLEX, `dices` the VGAM517 folded precursor RNA into VGAM517 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 48%) nucleotide sequence of VGAM517 RNA is designated SEQ ID:3228, and is provided hereinbelow with reference to the sequence listing part.

[23164] VGAM517 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM517 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM517 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23165] VGAM517 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM517 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM517 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM517 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM517 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23166] The complementary binding of VGAM517 RNA, herein designated VGAM RNA, to host target binding sites on VGAM517 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM517 host target RNA into VGAM517 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23167] It is appreciated that VGAM517 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM517 host target genes. The mRNA of each one of this plurality of VGAM517 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM517 RNA, herein designated VGAM RNA, and which when bound by VGAM517 RNA causes inhibition of translation of respective one or more VGAM517 host target proteins.

[23168] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM517 gene, herein designated VGAM GENE, on one or more VGAM517 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23169] It is yet further appreciated that a function of VGAM517 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM517 include diagnosis, prevention and treatment of viral infection by Galinsoga Mosaic Virus. Specific functions, and accordingly utilities, of VGAM517

correlate with, and may be deduced from, the identity of the host target genes which VGAM517 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23170] Nucleotide sequences of the VGAM517 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM517 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM517 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM517 are further described hereinbelow with reference to Table 1.

[23171] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM517 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM517 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23172] As mentioned hereinabove with reference to Fig. 1, a function of VGAM517 gene, herein designated VGAM is inhibition of expression of VGAM517 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM517 correlate with, and may be deduced



from, the identity of the target genes which VGAM517 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23173] Interleukin 18 Receptor 1 (IL18R1, Accession NM\_003855) is a VGAM517 host target gene. IL18R1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL18R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL18R1 BINDING SITE, designated SEQ ID:9950, to the nucleotide sequence of VGAM517 RNA, herein designated VGAM RNA, also designated SEQ ID:3228.

[23174] A function of VGAM517 is therefore inhibition of Interleukin 18 Receptor 1 (IL18R1, Accession NM\_003855), a gene which is required for dorsal-ventral embryonic polarity and promotes heterophilic cellular adhesion. Accordingly, utilities of VGAM517 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL18R1. The function of IL18R1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM37. Lunatic Fringe Ho-

molog (Drosophila) (LFNG, Accession XM\_166539) is another VGAM517 host target gene. LFNG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LFNG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LFNG BINDING SITE, designated SEQ ID:44511, to the nucleotide sequence of VGAM517 RNA, herein designated VGAM RNA, also designated SEQ ID:3228.

[23175] Another function of VGAM517 is therefore inhibition of Lunatic Fringe Homolog (Drosophila) (LFNG, Accession XM\_166539). Accordingly, utilities of VGAM517 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LFNG. HSPC014 (Accession NM\_015932) is another VGAM517 host target gene. HSPC014 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPC014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC014 BINDING SITE, designated SEQ ID:18053, to the nucleotide sequence of VGAM517 RNA,

herein designated VGAM RNA, also designated SEQ ID:3228.

[23176] Another function of VGAM517 is therefore inhibition of HSPC014 (Accession NM\_015932). Accordingly, utilities of VGAM517 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC014. KIAA0261 (Accession XM\_042946) is another VGAM517 host target gene. KIAA0261 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0261 BINDING SITE, designated SEQ ID:33834, to the nucleotide sequence of VGAM517 RNA, herein designated VGAM RNA, also designated SEQ ID:3228.

[23177] Another function of VGAM517 is therefore inhibition of KIAA0261 (Accession XM\_042946). Accordingly, utilities of VGAM517 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0261. KIAA1727 (Accession XM\_034262) is another VGAM517 host target gene. KIAA1727 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1727, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1727 BINDING SITE, designated SEQ ID:32028, to the nucleotide sequence of VGAM517 RNA, herein designated VGAM RNA, also designated SEQ ID:3228.

[23178] Another function of VGAM517 is therefore inhibition of KIAA1727 (Accession XM\_034262). Accordingly, utilities of VGAM517 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1727. LOC162333 (Accession XM\_102591) is another VGAM517 host target gene. LOC162333 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC162333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162333 BINDING SITE, designated SEQ ID:42120, to the nucleotide sequence of VGAM517 RNA, herein designated VGAM RNA, also designated SEQ ID:3228.

[23179] Another function of VGAM517 is therefore inhibition of LOC162333 (Accession XM\_102591). Accordingly, utilities

of VGAM517 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162333. LOC90906 (Accession XM\_034809) is another VGAM517 host target gene. LOC90906 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90906, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90906 BINDING SITE, designated SEQ ID:32154, to the nucleotide sequence of VGAM517 RNA, herein designated VGAM RNA, also designated SEQ ID:3228.

[23180] Another function of VGAM517 is therefore inhibition of LOC90906 (Accession XM\_034809). Accordingly, utilities of VGAM517 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90906. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 518 (VGAM518) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23181] VGAM518 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM518 was detected is described hereinabove with reference to Figs. 1–8.

[23182] VGAM518 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM518 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23183] VGAM518 gene encodes a VGAM518 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM518 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM518 precursor RNA is designated SEQ ID:504, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:504 is located at position 10108 relative to the genome of Lymphocystis Disease Virus 1.

[23184] VGAM518 precursor RNA folds onto itself, forming VGAM518 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23185] An enzyme complex designated DICER COMPLEX, `dices` the VGAM518 folded precursor RNA into VGAM518 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM518 RNA is designated SEQ ID:3229, and is provided hereinbelow with reference to the sequence listing part.

[23186] VGAM518 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM518 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM518 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[23187] VGAM518 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM518 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM518 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM518 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM518 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.



[23188] The complementary binding of VGAM518 RNA, herein designated VGAM RNA, to host target binding sites on VGAM518 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM518 host target RNA into VGAM518 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23189] It is appreciated that VGAM518 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM518 host target genes. The mRNA of each one of this plurality of VGAM518 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM518 RNA, herein designated VGAM RNA, and which when bound by VGAM518 RNA causes inhibition of translation of respective one or more VGAM518 host target proteins.

[23190] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM518 gene, herein designated VGAM GENE, on one or more VGAM518 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23191] It is yet further appreciated that a function of VGAM518 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of viral infection by Lymphocystis Disease Virus 1. Specific functions, and accordingly utilities, of VGAM518 correlate with, and may be deduced from, the identity of the host target genes which VGAM518 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23192] Nucleotide sequences of the VGAM518 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM518 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM518 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM518 are further  
described hereinbelow with reference to Table 1.

[23193] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM518 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM518 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[23194] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM518 gene, herein designated VGAM is  
inhibition of expression of VGAM518 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM518 correlate with, and may be deduced  
from, the identity of the target genes which VGAM518  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[23195] IL2-inducible T-cell Kinase (ITK, Accession NM\_005546) is  
a VGAM518 host target gene. ITK BINDING SITE is HOST

TARGET binding site found in the 3` untranslated region of mRNA encoded by ITK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITK BINDING SITE, designated SEQ ID:12079, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23196] A function of VGAM518 is therefore inhibition of IL2-inducible T-cell Kinase (ITK, Accession NM\_005546), a gene which plays a role in t cell proliferation and differentiation. Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITK. The function of ITK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM288. Platelet-derived Growth Factor Receptor, Beta Polypeptide (PDGFRB, Accession XM\_038350) is another VGAM518 host target gene. PDGFRB BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PDGFRB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of PDGFRB BINDING SITE, designated SEQ ID:32819, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23197] Another function of VGAM518 is therefore inhibition of Platelet-derived Growth Factor Receptor, Beta Polypeptide (PDGFRB, Accession XM\_038350), a gene which Platelet-derived growth factor receptor beta chain; tyrosine kinase receptor. Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDGFRB. The function of PDGFRB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM125.Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736) is another VGAM518 host target gene. XPR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XPR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XPR1 BINDING SITE, designated SEQ

ID:11126, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23198] Another function of VGAM518 is therefore inhibition of Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736), a gene which is a putative G protein-coupled receptor and a target for xenotropic and polytropic murine leukemia retroviruses. Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XPR1. The function of XPR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM430. Chromosome 5 Open Reading Frame 7 (C5orf7, Accession XM\_033576) is another VGAM518 host target gene. C5orf7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C5orf7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C5orf7 BINDING SITE, designated SEQ ID:31941, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3229.

[23199] Another function of VGAM518 is therefore inhibition of Chromosome 5 Open Reading Frame 7 (C5orf7, Accession XM\_033576). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C5orf7. DT1P1A10 (Accession XM\_029187) is another VGAM518 host target gene. DT1P1A10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DT1P1A10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DT1P1A10 BINDING SITE, designated SEQ ID:30857, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23200] Another function of VGAM518 is therefore inhibition of DT1P1A10 (Accession XM\_029187). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DT1P1A10. Echinoderm Microtubule Associated Protein Like 4 (EML4, Accession NM\_019063) is another VGAM518 host target gene. EML4 BINDING SITE is HOST TARGET

binding site found in the 3` untranslated region of mRNA encoded by EML4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EML4 BINDING SITE, designated SEQ ID:21147, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23201] Another function of VGAM518 is therefore inhibition of Echinoderm Microtubule Associated Protein Like 4 (EML4, Accession NM\_019063). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EML4. Erythrocyte Membrane Protein Band 4.1-like 1 (EPB41L1, Accession XM\_047295) is another VGAM518 host target gene. EPB41L1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by EPB41L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPB41L1 BINDING SITE, designated SEQ ID:34943, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ



ID:3229.

[23202] Another function of VGAM518 is therefore inhibition of Erythrocyte Membrane Protein Band 4.1-like 1 (EPB41L1, Accession XM\_047295). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPB41L1. FLJ10583 (Accession NM\_018148) is another VGAM518 host target gene. FLJ10583 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10583, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10583 BINDING SITE, designated SEQ ID:19951, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23203] Another function of VGAM518 is therefore inhibition of FLJ10583 (Accession NM\_018148). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10583. FLJ20154 (Accession XM\_053688) is another VGAM518 host target gene. FLJ20154 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA

encoded by FLJ20154, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20154 BINDING SITE, designated SEQ ID:36107, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23204] Another function of VGAM518 is therefore inhibition of FLJ20154 (Accession XM\_053688). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20154. Heat Shock Transcription Factor 2 (HSF2, Accession NM\_004506) is another VGAM518 host target gene. HSF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSF2 BINDING SITE, designated SEQ ID:10838, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23205] Another function of VGAM518 is therefore inhibition of Heat Shock Transcription Factor 2 (HSF2, Accession

NM\_004506). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSF2. KIAA1323 (Accession XM\_032146) is another VGAM518 host target gene.

KIAA1323 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1323, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1323 BINDING SITE, designated SEQ ID:31570, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23206] Another function of VGAM518 is therefore inhibition of KIAA1323 (Accession XM\_032146). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1323. Nuclear Receptor Subfamily 6, Group A, Member 1 (NR6A1, Accession NM\_033334) is another VGAM518 host target gene. NR6A1 BINDING SITE1 through NR6A1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by NR6A1, corresponding to HOST TARGET binding sites

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR6A1 BINDING SITE1 through NR6A1 BINDING SITE3, designated SEQ ID:27182, SEQ ID:27188 and SEQ ID:7234 respectively, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23207] Another function of VGAM518 is therefore inhibition of Nuclear Receptor Subfamily 6, Group A, Member 1 (NR6A1, Accession NM\_033334). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR6A1. LOC158235 (Accession XM\_098897) is another VGAM518 host target gene. LOC158235 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158235, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158235 BINDING SITE, designated SEQ ID:41925, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23208] Another function of VGAM518 is therefore inhibition of

LOC158235 (Accession XM\_098897). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158235. LOC158434 (Accession XM\_098939) is another VGAM518 host target gene. LOC158434 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158434, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158434 BINDING SITE, designated SEQ ID:41988, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23209] Another function of VGAM518 is therefore inhibition of LOC158434 (Accession XM\_098939). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158434. LOC203350 (Accession XM\_117536) is another VGAM518 host target gene. LOC203350 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC203350 BINDING SITE, designated SEQ ID:43536, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23210] Another function of VGAM518 is therefore inhibition of LOC203350 (Accession XM\_117536). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203350. LOC219529 (Accession XM\_167563) is another VGAM518 host target gene. LOC219529 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219529, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219529 BINDING SITE, designated SEQ ID:44674, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23211] Another function of VGAM518 is therefore inhibition of LOC219529 (Accession XM\_167563). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219529. LOC253613 (Accession XM\_171225) is an-

other VGAM518 host target gene. LOC253613 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253613, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253613 BINDING SITE, designated SEQ ID:46009, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23212] Another function of VGAM518 is therefore inhibition of LOC253613 (Accession XM\_171225). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253613. LOC255252 (Accession XM\_170779) is another VGAM518 host target gene. LOC255252 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255252, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255252 BINDING SITE, designated SEQ ID:45549, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23213] Another function of VGAM518 is therefore inhibition of LOC255252 (Accession XM\_170779). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255252. LOC90750 (Accession XM\_033868) is another VGAM518 host target gene. LOC90750 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90750 BINDING SITE, designated SEQ ID:31969, to the nucleotide sequence of VGAM518 RNA, herein designated VGAM RNA, also designated SEQ ID:3229.

[23214] Another function of VGAM518 is therefore inhibition of LOC90750 (Accession XM\_033868). Accordingly, utilities of VGAM518 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90750. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 519 (VGAM519) viral gene, which modulates expression of respective host target genes thereof,



the function and utility of which host target genes is known in the art.

[23215] VGAM519 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM519 was detected is described hereinabove with reference to Figs. 1–8.

[23216] VGAM519 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM519 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23217] VGAM519 gene encodes a VGAM519 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM519 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM519 precursor RNA is designated SEQ ID:505, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:505 is located at position 70833 relative to the genome of Lymphocystis Disease Virus 1.

[23218] VGAM519 precursor RNA folds onto itself, forming VGAM519 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[23219] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM519 folded precursor RNA into VGAM519 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM519 RNA is designated SEQ ID:3230, and  
is provided hereinbelow with reference to the sequence  
listing part.

[23220] VGAM519 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM519 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM519 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23221] VGAM519 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM519 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM519 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM519 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM519 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23222] The complementary binding of VGAM519 RNA, herein designated VGAM RNA, to host target binding sites on VGAM519 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM519 host target RNA into VGAM519 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23223] It is appreciated that VGAM519 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM519 host target genes. The mRNA of each one of this plurality of VGAM519 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM519 RNA, herein designated VGAM RNA, and which when bound by VGAM519 RNA causes inhibition of translation of respective one or more VGAM519 host target proteins.

[23224] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM519 gene, herein designated VGAM GENE, on one or more VGAM519 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23225] It is yet further appreciated that a function of VGAM519 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM519 include diagnosis, prevention and treatment of viral infection by Lymphocystis Disease Virus 1. Specific functions, and accordingly utilities, of VGAM519 correlate with, and may be deduced from, the identity of the host target genes which VGAM519 binds and inhibits, and the function of these host target genes,

as elaborated hereinbelow.

[23226] Nucleotide sequences of the VGAM519 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM519 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM519 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM519 are further described hereinbelow with reference to Table 1.

[23227] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM519 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM519 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23228] As mentioned hereinabove with reference to Fig. 1, a function of VGAM519 gene, herein designated VGAM is inhibition of expression of VGAM519 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM519 correlate with, and may be deduced from, the identity of the target genes which VGAM519 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23229] Solute Carrier Family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), Member 1 (SLC1A1, Accession NM\_004170) is a VGAM519 host target gene. SLC1A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC1A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC1A1 BINDING SITE, designated SEQ ID:10378, to the nucleotide sequence of VGAM519 RNA, herein designated VGAM RNA, also designated SEQ ID:3230.

[23230] A function of VGAM519 is therefore inhibition of Solute Carrier Family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), Member 1 (SLC1A1, Accession NM\_004170), a gene which is a glutamate transporter, essential for terminating the postsynaptic action of glutamate by rapidly removing it from the synaptic cleft. Accordingly, utilities of VGAM519 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC1A1. The function of SLC1A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described

hereinabove with reference to VGAM206.DKFZP566B183 (Accession NM\_015509) is another VGAM519 host target gene. DKFZP566B183 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP566B183, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566B183 BINDING SITE, designated SEQ ID:17766, to the nucleotide sequence of VGAM519 RNA, herein designated VGAM RNA, also designated SEQ ID:3230.

[23231] Another function of VGAM519 is therefore inhibition of DKFZP566B183 (Accession NM\_015509). Accordingly, utilities of VGAM519 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566B183. FLJ00024 (Accession XM\_033361) is another VGAM519 host target gene. FLJ00024 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ00024, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ00024 BINDING SITE, designated SEQ ID:31886, to the



nucleotide sequence of VGAM519 RNA, herein designated VGAM RNA, also designated SEQ ID:3230.

[23232] Another function of VGAM519 is therefore inhibition of FLJ00024 (Accession XM\_033361). Accordingly, utilities of VGAM519 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00024. RAB3-GAP150 (Accession NM\_012414) is another VGAM519 host target gene. RAB3-GAP150 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB3-GAP150, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB3-GAP150 BINDING SITE, designated SEQ ID:14789, to the nucleotide sequence of VGAM519 RNA, herein designated VGAM RNA, also designated SEQ ID:3230.

[23233] Another function of VGAM519 is therefore inhibition of RAB3-GAP150 (Accession NM\_012414). Accordingly, utilities of VGAM519 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB3-GAP150. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic

Address Messenger 520 (VGAM520) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23234] VGAM520 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM520 was detected is described hereinabove with reference to Figs. 1–8.

[23235] VGAM520 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM520 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23236] VGAM520 gene encodes a VGAM520 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM520 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM520 precursor RNA is designated SEQ ID:506, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:506 is located at position 71198 relative to the genome of Lymphocystis Disease Virus 1.

[23237] VGAM520 precursor RNA folds onto itself, forming VGAM520 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23238] An enzyme complex designated DICER COMPLEX, `dices` the VGAM520 folded precursor RNA into VGAM520 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM520 RNA is designated SEQ ID:3231, and is provided hereinbelow with reference to the sequence listing part.

[23239] VGAM520 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM520 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM520 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23240] VGAM520 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM520 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM520 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM520 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM520 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23241] The complementary binding of VGAM520 RNA, herein designated VGAM RNA, to host target binding sites on VGAM520 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM520 host target RNA into VGAM520 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23242] It is appreciated that VGAM520 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM520 host target genes. The mRNA of each one of this plurality of VGAM520 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM520 RNA, herein designated VGAM RNA, and which when bound by VGAM520 RNA causes inhibition of translation of respective one or more VGAM520 host target proteins.

[23243] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM520 gene, herein designated VGAM GENE, on one or more VGAM520 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23244] It is yet further appreciated that a function of VGAM520 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM520 include diagnosis, prevention and treatment of viral infection by Lymphocystis Disease Virus 1. Specific functions, and accordingly utilities, of VGAM520 correlate with, and may be deduced from, the

identity of the host target genes which VGAM520 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23245] Nucleotide sequences of the VGAM520 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM520 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM520 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM520 are further described hereinbelow with reference to Table 1.

[23246] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM520 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM520 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23247] As mentioned hereinabove with reference to Fig. 1, a function of VGAM520 gene, herein designated VGAM is inhibition of expression of VGAM520 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM520 correlate with, and may be deduced from, the identity of the target genes which VGAM520

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23248] Nuclear Antigen Sp100 (SP100, Accession NM\_003113) is a VGAM520 host target gene. SP100 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SP100, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SP100 BINDING SITE, designated SEQ ID:9085, to the nucleotide sequence of VGAM520 RNA, herein designated VGAM RNA, also designated SEQ ID:3231.

[23249] A function of VGAM520 is therefore inhibition of Nuclear Antigen Sp100 (SP100, Accession NM\_003113), a gene which may be involved in transduction of interferon action. Accordingly, utilities of VGAM520 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SP100. The function of SP100 has been established by previous studies. Seeler et al. (1998) showed that SP100 complexes with members of the HP1 family of nonhistone chromosomal proteins (e.g., CBX5, 604478). A variant of SP100, termed SP100B by the authors, contains additional 3-prime sequence encoding a



688-amino acid protein. A splice variant of SP100B, termed SP100-HMG, is joined to an 81-amino acid HMG1 (OMIM Ref. No. 163905)-like peptide by a 14-amino acid bridge. The HMG1-like domain is 87% identical and 93% similar to HMG1. SP100-HMG has the potential to be a DNA-binding protein. All 3 variants, SP100, SP100B, and SP100-HMG, colocalize with HP1 in NBs, suggesting that the N-terminal portion of SP100 is responsible for the interaction. HP1 expression is enhanced when SP100 synthesis is induced by interferon. By Northern blot analysis, Dent et al. (1996) found that SP100B, which they called LYSP100, is expressed only in lymphoid tissues (spleen, tonsil, and thymus), mature B-cell lines, and some T-cell lines, but not in brain, liver, muscle, or nonlymphoid cell lines. They noted that SP100 expression is widespread. By confocal immunofluorescence microscopy, they determined that a minority of the nuclear dots for SP100B overlapped with SP100 and PML, whereas most localized to another class of subnuclear structures, which they termed LANDs (LYSP100-associated nuclear domains), which are morphologically and spatially distinct from PML NBs.

[23250] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [23251] Seeler, J. S.; Marchio, A.; Sitterlin, D.; Transy, C.; Dejean, A. : Interaction of SP100 with HP1 proteins: a link between the promyelocytic leukemia-associated nuclear bodies and the chromatin compartment. *Proc. Nat. Acad. Sci.* 95: 7316–7321, 1998. ; and
- [23252] Dent, A. L.; Yewdell, J.; Puvion-Dutilleul, F.; Koken, M. H.; de The, H.; Staudt, L. M. : LYSP100 associated nuclear domains (LANDs): description of a new class of subnuclear structures a.
- [23253] Further studies establishing the function and utilities of SP100 are found in John Hopkins OMIM database record ID 604585, and in cited publications numbered 4943–494 and 4547 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Calcium/calmodulin-dependent Protein Kinase Kinase 2, Beta (CAMKK2, Accession NM\_006549) is another VGAM520 host target gene. CAMKK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAMKK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

complementarity of the nucleotide sequences of CAMKK2 BINDING SITE, designated SEQ ID:13314, to the nucleotide sequence of VGAM520 RNA, herein designated VGAM RNA, also designated SEQ ID:3231.

[23254] Another function of VGAM520 is therefore inhibition of Calcium/calmodulin-dependent Protein Kinase Kinase 2, Beta (CAMKK2, Accession NM\_006549). Accordingly, utilities of VGAM520 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAMKK2. KIAA0449 (Accession NM\_017596) is another VGAM520 host target gene. KIAA0449 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0449, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0449 BINDING SITE, designated SEQ ID:19058, to the nucleotide sequence of VGAM520 RNA, herein designated VGAM RNA, also designated SEQ ID:3231.

[23255] Another function of VGAM520 is therefore inhibition of KIAA0449 (Accession NM\_017596). Accordingly, utilities of VGAM520 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0449. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 521 (VGAM521) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23256] VGAM521 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM521 was detected is described hereinabove with reference to Figs. 1–8.

[23257] VGAM521 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM521 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23258] VGAM521 gene encodes a VGAM521 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM521 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM521 precursor RNA is designated SEQ ID:507, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:507 is located at position 75552 relative to the genome of Lymphocystis Disease Virus 1.

[23259] VGAM521 precursor RNA folds onto itself, forming VGAM521 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23260] An enzyme complex designated DICER COMPLEX, `dices` the VGAM521 folded precursor RNA into VGAM521 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM521 RNA is designated SEQ ID:3232, and is provided hereinbelow with reference to the sequence listing part.

[23261] VGAM521 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM521 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM521 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23262] VGAM521 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM521 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM521 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM521 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM521 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23263] The complementary binding of VGAM521 RNA, herein designated VGAM RNA, to host target binding sites on VGAM521 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM521 host target RNA into VGAM521 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23264] It is appreciated that VGAM521 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM521 host target genes. The mRNA of each one of this plurality of VGAM521 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM521 RNA, herein designated VGAM RNA, and which when bound by VGAM521 RNA causes in-

hibition of translation of respective one or more VGAM521 host target proteins.

[23265] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM521 gene, herein designated VGAM GENE, on one or more VGAM521 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23266] It is yet further appreciated that a function of VGAM521 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM521 include diagnosis, prevention and



treatment of viral infection by Lymphocystis Disease Virus

1. Specific functions, and accordingly utilities, of VGAM521 correlate with, and may be deduced from, the identity of the host target genes which VGAM521 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23267] Nucleotide sequences of the VGAM521 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM521 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM521 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM521 are further described hereinbelow with reference to Table 1.

[23268] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM521 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM521 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23269] As mentioned hereinabove with reference to Fig. 1, a function of VGAM521 gene, herein designated VGAM is inhibition of expression of VGAM521 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM521 correlate with, and may be deduced from, the identity of the target genes which VGAM521 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23270] Neuro-oncological Ventral Antigen 1 (NOVA1, Accession NM\_002515) is a VGAM521 host target gene. NOVA1 BINDING SITE1 and NOVA1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by NOVA1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NOVA1 BINDING SITE1 and NOVA1 BINDING SITE2, designated SEQ ID:8348 and SEQ ID:13217 respectively, to the nucleotide sequence of VGAM521 RNA, herein designated VGAM RNA, also designated SEQ ID:3232.

[23271] A function of VGAM521 is therefore inhibition of Neuro-oncological Ventral Antigen 1 (NOVA1, Accession NM\_002515), a gene which may regulate rna splicing or metabolism in a specific subset of developing neurons. Accordingly, utilities of VGAM521 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with NOVA1. The function of NOVA1 has been established by previous studies. Using antisera from patients with a paraneoplastic neurologic disorder involving the subcortical motor system, Buckanovich et al. (1993) identified a gene that they termed NOVA1. The NOVA1 gene encodes a neuron-specific RNA-binding protein that is inhibited by paraneoplastic antibodies (Buckanovich et al., 1996). Fletcher et al. (1997) showed that the mouse homolog maps to mouse chromosome 12 and suggested that the human gene is probably located on 14q. See also NOVA2 (OMIM Ref. No. 601991). Prestigiacomo et al. (2001) described a patient with a history of bladder carcinoma (OMIM Ref. No. 109800) who presented with the opsoclonus-ataxia syndrome. They demonstrated the presence of anti-Ri antibodies in the patient's serum and cerebrospinal fluid and found that the target Ri antigen was expressed in the original tumor specimen. This may have been the first instance of the syndrome with bladder cancer; it has been associated in children with neuroblastoma and in adults with breast carcinoma and gynecologic malignancies.

[23272] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [23273] Buckanovich, R. J.; Posner, J. B.; Darnell, R. B. : Nova, the paraneoplastic Ri antigen, is homologous to an RNA-binding protein and is specifically expressed in the developing motor system. *Neuron* 11: 657–672, 1993. ; and
- [23274] Prestigiacomo, C. J.; Balmaceda, C.; Dalmau, J. : Anti-Ri-associated paraneoplastic opsoclonus-ataxia syndrome in a man with transitional cell carcinoma: a case report. *Cancer* 91: 1423–.
- [23275] Further studies establishing the function and utilities of NOVA1 are found in John Hopkins OMIM database record ID 602157, and in cited publications numbered 5989–5990, 2386, 481 and 5991 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 522 (VGAM522) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [23276] VGAM522 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM522 was detected is described hereinabove with reference to Figs. 1–8.

[23277] VGAM522 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM522 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23278] VGAM522 gene encodes a VGAM522 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM522 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM522 precursor RNA is designated SEQ ID:508, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:508 is located at position 76141 relative to the genome of Lymphocystis Disease Virus 1.

[23279] VGAM522 precursor RNA folds onto itself, forming VGAM522 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23280] An enzyme complex designated DICER COMPLEX, `dices` the VGAM522 folded precursor RNA into VGAM522 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM522 RNA is designated SEQ ID:3233, and is provided hereinbelow with reference to the sequence listing part.

[23281] VGAM522 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM522 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM522 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23282] VGAM522 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM522 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM522 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM522 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM522 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23283] The complementary binding of VGAM522 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM522 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM522 host target RNA into VGAM522 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23284] It is appreciated that VGAM522 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM522 host target genes. The mRNA of each one of this plurality of VGAM522 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM522 RNA, herein designated VGAM RNA, and which when bound by VGAM522 RNA causes inhibition of translation of respective one or more VGAM522 host target proteins.

[23285] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM522 gene, herein designated VGAM GENE, on one or more VGAM522 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove



with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23286] It is yet further appreciated that a function of VGAM522 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM522 include diagnosis, prevention and treatment of viral infection by Lymphocystis Disease Virus 1. Specific functions, and accordingly utilities, of VGAM522 correlate with, and may be deduced from, the identity of the host target genes which VGAM522 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23287] Nucleotide sequences of the VGAM522 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM522 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM522 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM522 are further described hereinbelow with reference to Table 1.

[23288] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM522 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM522 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23289] As mentioned hereinabove with reference to Fig. 1, a function of VGAM522 gene, herein designated VGAM is inhibition of expression of VGAM522 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM522 correlate with, and may be deduced from, the identity of the target genes which VGAM522 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23290] UDP-GlcNAc:betaGal Beta-

1,3-N-acetylglucosaminyltransferase 5 (B3GNT5, Accession NM\_032047) is a VGAM522 host target gene.

B3GNT5 BINDING SITE is HOST TARGET binding site found

in the 3` untranslated region of mRNA encoded by B3GNT5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B3GNT5 BINDING SITE, designated SEQ ID:25764, to the nucleotide sequence of VGAM522 RNA, herein designated VGAM RNA, also designated SEQ ID:3233.

[23291] A function of VGAM522 is therefore inhibition of UDP-GlcNAc:betaGal Beta-1,3-N-acetylglucosaminyltransferase 5 (B3GNT5, Accession NM\_032047). Accordingly, utilities of VGAM522 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B3GNT5. LOC154007 (Accession XM\_087824) is another VGAM522 host target gene. LOC154007 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC154007, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154007 BINDING SITE, designated SEQ ID:39457, to the nucleotide sequence of VGAM522 RNA, herein designated VGAM RNA, also designated SEQ ID:3233.

[23292] Another function of VGAM522 is therefore inhibition of LOC154007 (Accession XM\_087824). Accordingly, utilities of VGAM522 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154007. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 523 (VGAM523) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23293] VGAM523 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM523 was detected is described hereinabove with reference to Figs. 1–8.

[23294] VGAM523 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM523 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23295] VGAM523 gene encodes a VGAM523 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM523

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM523 precursor RNA is designated SEQ ID:509, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:509 is located at position 44554 relative to the genome of Murid Herpesvirus 4.

[23296] VGAM523 precursor RNA folds onto itself, forming VGAM523 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23297] An enzyme complex designated DICER COMPLEX, `dices` the VGAM523 folded precursor RNA into VGAM523 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 40%) nucleotide sequence of VGAM523 RNA is designated SEQ ID:3234, and is provided hereinbelow with reference to the sequence listing part.

[23298] VGAM523 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM523 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM523 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[23299] VGAM523 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM523 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM523 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM523 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM523 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23300] The complementary binding of VGAM523 RNA, herein designated VGAM RNA, to host target binding sites on VGAM523 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM523 host target RNA into VGAM523 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23301] It is appreciated that VGAM523 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM523 host target genes. The mRNA of each one of this plurality of VGAM523 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM523 RNA, herein designated VGAM RNA, and which when bound by VGAM523 RNA causes inhibition of translation of respective one or more VGAM523 host target proteins.

[23302] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM523 gene, herein designated VGAM GENE, on one or more VGAM523 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).



[23303] It is yet further appreciated that a function of VGAM523 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM523 correlate with, and may be deduced from, the identity of the host target genes which VGAM523 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23304] Nucleotide sequences of the VGAM523 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM523 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM523 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM523 are further described hereinbelow with reference to Table 1.

[23305] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM523 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM523 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[23306] As mentioned hereinabove with reference to Fig. 1, a function of VGAM523 gene, herein designated VGAM is inhibition of expression of VGAM523 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM523 correlate with, and may be deduced from, the identity of the target genes which VGAM523 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23307] Jumonji Homolog (mouse) (JMJ, Accession NM\_004973) is a VGAM523 host target gene. JMJ BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by JMJ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JMJ BINDING SITE, designated SEQ ID:11418, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23308] A function of VGAM523 is therefore inhibition of Jumonji Homolog (mouse) (JMJ, Accession NM\_004973), a gene which participates in the negative regulation of cell growth. Accordingly, utilities of VGAM523 include diagno-

sis, prevention and treatment of diseases and clinical conditions associated with JMJ. The function of JMJ has been established by previous studies. Berge-Lefranc et al. (1996) isolated clones highly homologous to the mouse gene jumonji from a human embryonic cDNA library. In mouse, jumonji (jnj) is required for neural tube formation. Berge-Lefranc et al. (1996) reported that the human jumonji (JMJ) and mouse jnj gene products are 90% identical. Northern blot analysis revealed a low level of expression of JMJ in all human embryonic and adult tissues analyzed. In situ hybridization studies on embryonic slices revealed high levels of expression in dorsal root ganglia neurons. The authors detected high levels of expression in adult cerebral cortex. Toyoda et al. (2000) determined that JMJ is expressed as a 160-kD protein by Western blot analysis. Immunofluorescence and Western blot analysis demonstrated that JMJ specifically localizes to the cell nucleus. Overexpression of JMJ appeared to inhibit cell growth, whereas Jnj-deficient mice had cell growth enhancement. Berge-Lefranc et al. (1996) mapped the human JMJ gene to chromosome 6p24-p23 using autoradiographic in situ hybridization

[23309] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [23310] Berge-Lefranc, J.-L.; Jay, P.; Massacrier, A.; Cau, P.; Mattei, M. G.; Bauer, S.; Marsollier, C.; Berta, P.; Fontes, M. : Characterization of the human jumonji gene. Hum. Molec. Genet. 5: 1637-1641, 1996. ; and
- [23311] Toyoda, M.; Kojima, M.; Takeuchi, T. : Jumonji is a nuclear protein that participates in the negative regulation of cell growth. Biochem. Biophys. Res. Commun. 274: 332-336, 2000.
- [23312] Further studies establishing the function and utilities of JMJ are found in John Hopkins OMIM database record ID 601594, and in cited publications numbered 1286-1287 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010) is another VGAM523 host target gene. NRCAM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRCAM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRCAM BINDING SITE, designated SEQ ID:11452, to the nucleotide se-

quence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23313] Another function of VGAM523 is therefore inhibition of Neuronal Cell Adhesion Molecule (NRCAM, Accession NM\_005010), a gene which functions as a cell surface protein and belongs to the immunoglobulin superfamily. Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRCAM. The function of NRCAM and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM268.DKFZp564I1922 (Accession NM\_015419) is another VGAM523 host target gene. DKFZp564I1922 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp564I1922, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp564I1922 BINDING SITE, designated SEQ ID:17722, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23314] Another function of VGAM523 is therefore inhibition of

DKFZp564I1922 (Accession NM\_015419). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp564I1922. FLJ10097 (Accession XM\_043653) is another VGAM523 host target gene. FLJ10097 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10097, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10097 BINDING SITE, designated SEQ ID:33988, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23315] Another function of VGAM523 is therefore inhibition of FLJ10097 (Accession XM\_043653). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10097. FLJ20276 (Accession NM\_017738) is another VGAM523 host target gene. FLJ20276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ20276 BINDING SITE, designated SEQ ID:19327, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23316] Another function of VGAM523 is therefore inhibition of FLJ20276 (Accession NM\_017738). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20276. KIAA0825 (Accession XM\_027906) is another VGAM523 host target gene. KIAA0825 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0825, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0825 BINDING SITE, designated SEQ ID:30592, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23317] Another function of VGAM523 is therefore inhibition of KIAA0825 (Accession XM\_027906). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0825. LOC149153 (Accession XM\_097599) is another

VGAM523 host target gene. LOC149153 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149153, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149153 BINDING SITE, designated SEQ ID:40962, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23318] Another function of VGAM523 is therefore inhibition of LOC149153 (Accession XM\_097599). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149153. LOC200563 (Accession XM\_117251) is another VGAM523 host target gene. LOC200563 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200563, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200563 BINDING SITE, designated SEQ ID:43318, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.



[23319] Another function of VGAM523 is therefore inhibition of LOC200563 (Accession XM\_117251). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200563. LOC219627 (Accession XM\_166402) is another VGAM523 host target gene. LOC219627 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219627, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219627 BINDING SITE, designated SEQ ID:44272, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23320] Another function of VGAM523 is therefore inhibition of LOC219627 (Accession XM\_166402). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219627. LOC221814 (Accession XM\_168226) is another VGAM523 host target gene. LOC221814 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221814, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221814 BINDING SITE, designated SEQ ID:45088, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23321] Another function of VGAM523 is therefore inhibition of LOC221814 (Accession XM\_168226). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221814. LOC257415 (Accession XM\_171177) is another VGAM523 host target gene. LOC257415 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257415, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257415 BINDING SITE, designated SEQ ID:45957, to the nucleotide sequence of VGAM523 RNA, herein designated VGAM RNA, also designated SEQ ID:3234.

[23322] Another function of VGAM523 is therefore inhibition of LOC257415 (Accession XM\_171177). Accordingly, utilities of VGAM523 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC257415. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 524 (VGAM524) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23323] VGAM524 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM524 was detected is described hereinabove with reference to Figs. 1–8.

[23324] VGAM524 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM524 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23325] VGAM524 gene encodes a VGAM524 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM524 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM524 precursor RNA is designated SEQ ID:510, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:510 is located at position 45166 relative to the genome of Murid Herpesvirus 4.

[23326] VGAM524 precursor RNA folds onto itself, forming VGAM524 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23327] An enzyme complex designated DICER COMPLEX, `dices` the VGAM524 folded precursor RNA into VGAM524 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM524 RNA is designated SEQ ID:3235, and is provided hereinbelow with reference to the sequence listing part.

[23328] VGAM524 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM524 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM524 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23329] VGAM524 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM524 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM524 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM524 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM524 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23330] The complementary binding of VGAM524 RNA, herein designated VGAM RNA, to host target binding sites on VGAM524 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM524 host target RNA into VGAM524 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23331] It is appreciated that VGAM524 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM524 host target genes. The mRNA of each one of this plurality of VGAM524 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM524 RNA, herein designated VGAM RNA, and which when bound by VGAM524 RNA causes in-

hibition of translation of respective one or more VGAM524 host target proteins.

[23332] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM524 gene, herein designated VGAM GENE, on one or more VGAM524 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23333] It is yet further appreciated that a function of VGAM524 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM524 include diagnosis, prevention and

treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM524 correlate with, and may be deduced from, the identity of the host target genes which VGAM524 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [23334] Nucleotide sequences of the VGAM524 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM524 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM524 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM524 are further described hereinbelow with reference to Table 1.
- [23335] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM524 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM524 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [23336] As mentioned hereinabove with reference to Fig. 1, a function of VGAM524 gene, herein designated VGAM is inhibition of expression of VGAM524 target genes. It is



appreciated that specific functions, and accordingly utilities, of VGAM524 correlate with, and may be deduced from, the identity of the target genes which VGAM524 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23337] Heterogeneous Nuclear Ribonucleoprotein K (HNRPK, Accession NM\_002140) is a VGAM524 host target gene. HNRPK BINDING SITE1 and HNRPK BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HNRPK, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HNRPK BINDING SITE1 and HNRPK BINDING SITE2, designated SEQ ID:7916 and SEQ ID:25280 respectively, to the nucleotide sequence of VGAM524 RNA, herein designated VGAM RNA, also designated SEQ ID:3235.

[23338] A function of VGAM524 is therefore inhibition of Heterogeneous Nuclear Ribonucleoprotein K (HNRPK, Accession NM\_002140), a gene which play a role in the nuclear metabolism of hnrnas, particularly for pre-mrnas that contain cytidine-rich sequence. Accordingly, utilities of VGAM524 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with HNRPK. The function of HNRPK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM125.FLJ10546 (Accession XM\_002989) is another VGAM524 host target gene. FLJ10546 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10546, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10546 BINDING SITE, designated SEQ ID:29912, to the nucleotide sequence of VGAM524 RNA, herein designated VGAM RNA, also designated SEQ ID:3235.

[23339] Another function of VGAM524 is therefore inhibition of FLJ10546 (Accession XM\_002989). Accordingly, utilities of VGAM524 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10546. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 525 (VGAM525) viral gene, which modulates expression of respective host target genes thereof, the function and

utility of which host target genes is known in the art.

[23340] VGAM525 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM525 was detected is described hereinabove with reference to Figs. 1–8.

[23341] VGAM525 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM525 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23342] VGAM525 gene encodes a VGAM525 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM525 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM525 precursor RNA is designated SEQ ID:511, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:511 is located at position 53388 relative to the genome of Murid Herpesvirus 4.

[23343] VGAM525 precursor RNA folds onto itself, forming VGAM525 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[23344] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM525 folded precursor RNA into VGAM525 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 82%) nucleotide se-  
quence of VGAM525 RNA is designated SEQ ID:3236, and  
is provided hereinbelow with reference to the sequence  
listing part.

[23345] VGAM525 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM525 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM525 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[23346] VGAM525 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM525 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM525 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM525 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM525 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[23347] The complementary binding of VGAM525 RNA, herein designated VGAM RNA, to host target binding sites on VGAM525 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM525 host target RNA into VGAM525 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23348] It is appreciated that VGAM525 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM525 host target genes. The mRNA of each one of this plurality of VGAM525 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM525 RNA, herein designated VGAM RNA, and which when bound by VGAM525 RNA causes inhibition of translation of respective one or more VGAM525 host target proteins.

[23349] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM525 gene, herein designated VGAM GENE, on one or

more VGAM525 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23350] It is yet further appreciated that a function of VGAM525 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM525 correlate with, and may be deduced from, the identity of the host target genes which VGAM525 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [23351] Nucleotide sequences of the VGAM525 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM525 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM525 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM525 are further described hereinbelow with reference to Table 1.
- [23352] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM525 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM525 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [23353] As mentioned hereinabove with reference to Fig. 1, a function of VGAM525 gene, herein designated VGAM is inhibition of expression of VGAM525 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM525 correlate with, and may be deduced from, the identity of the target genes which VGAM525 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [23354] Amyloid Beta Precursor Protein (cytoplasmic tail) Binding



Protein 2 (APPBP2, Accession NM\_006380) is a VGAM525 host target gene. APPBP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APPBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APPBP2 BINDING SITE, designated SEQ ID:13077, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23355] A function of VGAM525 is therefore inhibition of Amyloid Beta Precursor Protein (cytoplasmic tail) Binding Protein 2 (APPBP2, Accession NM\_006380), a gene which interacts with the basolateral sorting signal of amyloid precursor protein. Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APPBP2. The function of APPBP2 has been established by previous studies. Epithelial cell surfaces are divided into apical and basolateral domains. The basolateral sorting of cell surface proteins depends on the presence of peptide-based basolateral sorting signals (BaSS) in the cytoplasmic domains of proteins. Amyloid precursor protein (APP; 104760), a basolat-

eral protein implicated in the pathogenesis of Alzheimer disease (AD; 104300), contains a tyrosine-based BaSS. Mutation of the tyrosine results in nonpolarized transport of APP. Using APP-BaSS as bait in a yeast 2-hybrid screen of a HeLa cell cDNA library, followed by negative selection with a tyr-ala mutant APP-BaSS as bait and 5-prime RACE, Zheng et al. (1998) isolated a cDNA encoding amyloid beta precursor protein-binding protein-2 (OMIM Ref. No. APPBP2), which they called PAT1 (protein interacting with APP tail-1). The deduced 585-amino acid hydrophilic APPBP2 protein, which is identical to the uncharacterized KIAA0228 protein identified by Nagase et al. (1996), lacks signal or transmembrane sequences but contains N- and C-terminal globular structures, a coiled coil domain, several protein kinase C phosphorylation sites, and 4 imperfect C-terminal tandem repeats. Binding analysis determined that APPBP2 binds specifically to the tyrosine-containing APP-BaSS and to the complete cytoplasmic domain of APP; it does not bind to mutant APP-BaSS. Western blot analysis showed that APPBP2 is present as a 70-kD protein in both cytosolic and, together with APP, membrane-associated cell fractions. Immunofluorescence microscopy demonstrated that APPBP2 is present in the

Golgi region and that its distribution overlaps that of APP. SDS-PAGE and immunoblotting showed that APPBP2 interacts with microtubules and is functionally associated with APP transport and/or processing. By Northern blot analysis, Nagase et al. (1996) detected ubiquitous expression of KIAA0228 as an approximately 6.5-kb transcript.

[23356] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23357] Nagase, T.; Seki, N.; Ishikawa, K.; Ohira, M.; Kawarabayasi, Y.; Ohara, O.; Tanaka, A.; Kotani, H.; Miyajima, N.; Nomura, N. : Prediction of the coding sequences of unidentified human genes. VI. The coding sequences of 80 new genes (KIAA0201–KIAA0280) deduced by analysis of cDNA clones from cell line KG–1 and brain. DNA Res. 3: 321–329, 1996. ; and

[23358] Zheng, P.; Eastman, J.; Vande Pol, S.; Pimplikar, S. W. : PAT1, a microtubule-interacting protein, recognizes the basolateral sorting signal of amyloid precursor protein. Proc. Nat. Aca.

[23359] Further studies establishing the function and utilities of APPBP2 are found in John Hopkins OMIM database record ID 605324, and in cited publications numbered 680 and

9379 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chondroitin Sulfate Proteoglycan 4 (melanoma-associated) (CSPG4, Accession NM\_001897) is another VGAM525 host target gene. CSPG4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSPG4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSPG4 BINDING SITE, designated SEQ ID:7624, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23360] Another function of VGAM525 is therefore inhibition of Chondroitin Sulfate Proteoglycan 4 (melanoma-associated) (CSPG4, Accession NM\_001897), a gene which plays a role in stabilizing cell-substratum interactions. Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSPG4. The function of CSPG4 has been established by previous studies. By N-terminal micropeptide sequence analysis, screening a melanoma cell line with a rat NG2 chondroitin sulfate proteoglycan

probe, and anchored PCR, Pluschke et al. (1996) isolated a cDNA encoding CSPG4, which they called MCSP. The deduced 2,322-amino acid protein has a signal sequence; 3 N-terminal domains defined by cysteine content; 15 potential N-linked glycosylation sites; a transmembrane segment containing a single cysteine; and a 75-residue cytoplasmic domain with 3 potential phosphorylation sites. Northern blot analysis revealed expression of a 9.0-kb transcript in melanoma cells; expression was not found in other tumors or normal tissues. In situ hybridization analysis demonstrated expression of CSPG4 in cells that stained with MCSP-specific monoclonal antibodies Smith et al. (1996) described the expression of a 220- to 240-kD cell-surface chondroitin sulfate proteoglycan molecule, previously described on human melanoma cells, and by amino acid sequencing identified it as the human homolog of the rat NG2 chondroitin sulfate proteoglycan molecule. They found that is not expressed by normal hematopoietic cells but is selectively expressed by leukemic blast cells from a subpopulation of children with acute myeloid leukemia who have a poor prognosis. These AML blasts have abnormalities in chromosome band 11q23, the site of the MLL gene (OMIM Ref. No. 159555).

The authors hypothesized that the gene that encodes the NG2 molecule is controlled by a transcription factor encoded by the MLL gene and that certain types of alterations in MLL result in the aberrant expression of the NG2 molecule. Behm et al. (1996) studied 104 consecutive children at initial presentation with acute lymphoblastic leukemia and concluded that the cell surface expression of NG2 is useful for identifying patients who have t(4;11) or t(11;19) translocations

[23361] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23362] Pluschke, G.; Vanek, M.; Evans, A.; Dittmar, T.; Schmid, P.; Itin, P.; Filardo, E. J.; Reisfeld, R. A. : Molecular cloning of a human melanoma-associated chondroitin sulfate proteoglycan. Proc. Nat. Acad. Sci. 93: 9710–9715, 1996. ; and

[23363] Behm, F. G.; Smith, F. O.; Raimondi, S. C.; Pui, C.–H.; Bernstein, I. D. : Human homologue of the rat chondroitin sulfate proteoglycan, NG2, detected by monoclonal antibody 7.1, identified.

[23364] Further studies establishing the function and utilities of CSPG4 are found in John Hopkins OMIM database record ID 601172, and in cited publications numbered

9309–9313 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fibronectin Leucine Rich Transmembrane Protein 2 (FLRT2, Accession NM\_013231) is another VGAM525 host target gene. FLRT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLRT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLRT2 BINDING SITE, designated SEQ ID:14876, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23365] Another function of VGAM525 is therefore inhibition of Fibronectin Leucine Rich Transmembrane Protein 2 (FLRT2, Accession NM\_013231), a gene which may have a function in cell adhesion and/or receptor signaling. Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLRT2. The function of FLRT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. Neural Precursor Cell Expressed,

Developmentally Down-regulated 4 (NEDD4, Accession XM\_046129) is another VGAM525 host target gene. NEDD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEDD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEDD4 BINDING SITE, designated SEQ ID:34690, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23366] Another function of VGAM525 is therefore inhibition of Neural Precursor Cell Expressed, Developmentally Down-regulated 4 (NEDD4, Accession XM\_046129), a gene which ubiquitinates regulatory proteins involved in transcription. Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEDD4. The function of NEDD4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM209. Dedicator of Cyto-kinesis 3 (DOCK3, Accession XM\_039259) is another VGAM525 host target gene. DOCK3 BINDING SITE is HOST



TARGET binding site found in the 3' untranslated region of mRNA encoded by DOCK3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DOCK3 BINDING SITE, designated SEQ ID:33039, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23367] Another function of VGAM525 is therefore inhibition of Dedicator of Cyto-kinesis 3 (DOCK3, Accession XM\_039259). Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DOCK3. FLJ20457 (Accession NM\_017832) is another VGAM525 host target gene. FLJ20457 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20457, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20457 BINDING SITE, designated SEQ ID:19495, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23368] Another function of VGAM525 is therefore inhibition of FLJ20457 (Accession NM\_017832). Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20457. KIAA0293 (Accession XM\_027045) is another VGAM525 host target gene. KIAA0293 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0293, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0293 BINDING SITE, designated SEQ ID:30397, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23369] Another function of VGAM525 is therefore inhibition of KIAA0293 (Accession XM\_027045). Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0293. KIAA0542 (Accession XM\_038520) is another VGAM525 host target gene. KIAA0542 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0542, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0542 BINDING SITE, designated SEQ ID:32859, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23370] Another function of VGAM525 is therefore inhibition of KIAA0542 (Accession XM\_038520). Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0542. KIAA1322 (Accession XM\_052626) is another VGAM525 host target gene. KIAA1322 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1322 BINDING SITE, designated SEQ ID:36018, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23371] Another function of VGAM525 is therefore inhibition of KIAA1322 (Accession XM\_052626). Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1322. LOC144559 (Accession XM\_084896) is another VGAM525 host target gene. LOC144559 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144559, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144559 BINDING SITE, designated SEQ ID:37763, to the nucleotide sequence of VGAM525 RNA, herein designated VGAM RNA, also designated SEQ ID:3236.

[23372] Another function of VGAM525 is therefore inhibition of LOC144559 (Accession XM\_084896). Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144559. LOC257041 (Accession XM\_173829) is another VGAM525 host target gene. LOC257041 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257041, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257041 BINDING SITE, designated SEQ ID:46563, to the nucleotide sequence of VGAM525 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3236.

[23373] Another function of VGAM525 is therefore inhibition of LOC257041 (Accession XM\_173829). Accordingly, utilities of VGAM525 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257041. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 526 (VGAM526) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23374] VGAM526 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM526 was detected is described hereinabove with reference to Figs. 1–8.

[23375] VGAM526 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM526 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23376] VGAM526 gene encodes a VGAM526 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM526 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM526 precursor RNA is designated SEQ ID:512, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:512 is located at position 54037 relative to the genome of Murid Herpesvirus 4.

[23377] VGAM526 precursor RNA folds onto itself, forming VGAM526 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23378] An enzyme complex designated DICER COMPLEX, `dices` the VGAM526 folded precursor RNA into VGAM526 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM526 RNA is designated SEQ ID:3237, and is provided hereinbelow with reference to the sequence listing part.

[23379] VGAM526 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM526 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM526 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[23380] VGAM526 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM526 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM526 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM526 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM526 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23381] The complementary binding of VGAM526 RNA, herein designated VGAM RNA, to host target binding sites on VGAM526 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM526 host target RNA into VGAM526 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23382] It is appreciated that VGAM526 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM526 host target genes. The mRNA of



each one of this plurality of VGAM526 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM526 RNA, herein designated VGAM RNA, and which when bound by VGAM526 RNA causes inhibition of translation of respective one or more VGAM526 host target proteins.

[23383] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM526 gene, herein designated VGAM GENE, on one or more VGAM526 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[23384] It is yet further appreciated that a function of VGAM526 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM526 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM526 correlate with, and may be deduced from, the identity of the host target genes which VGAM526 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23385] Nucleotide sequences of the VGAM526 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM526 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM526 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM526 are further described hereinbelow with reference to Table 1.

[23386] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM526 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM526 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[23387] As mentioned hereinabove with reference to Fig. 1, a function of VGAM526 gene, herein designated VGAM is inhibition of expression of VGAM526 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM526 correlate with, and may be deduced from, the identity of the target genes which VGAM526 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23388] LOC143888 (Accession XM\_084669) is a VGAM526 host target gene. LOC143888 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143888, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143888 BINDING SITE, designated SEQ ID:37666, to the nucleotide sequence of VGAM526 RNA, herein designated VGAM RNA, also designated SEQ ID:3237.

[23389] A function of VGAM526 is therefore inhibition of LOC143888 (Accession XM\_084669). Accordingly, utilities of VGAM526 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC143888. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 527 (VGAM527) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23390] VGAM527 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM527 was detected is described hereinabove with reference to Figs. 1–8.

[23391] VGAM527 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM527 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23392] VGAM527 gene encodes a VGAM527 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM527 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM527 precursor RNA is designated SEQ

ID:513, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:513 is located at position 83822 relative to the genome of Murid Herpesvirus 4.

[23393] VGAM527 precursor RNA folds onto itself, forming VGAM527 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23394] An enzyme complex designated DICER COMPLEX, `dices` the VGAM527 folded precursor RNA into VGAM527 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM527 RNA is designated SEQ ID:3238, and is provided hereinbelow with reference to the sequence

listing part.

[23395] VGAM527 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM527 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM527 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23396] VGAM527 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM527 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM527 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM527 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM527 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23397] The complementary binding of VGAM527 RNA, herein designated VGAM RNA, to host target binding sites on VGAM527 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM527 host target RNA into VGAM527 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23398] It is appreciated that VGAM527 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM527 host target genes. The mRNA of each one of this plurality of VGAM527 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM527 RNA, herein designated VGAM

RNA, and which when bound by VGAM527 RNA causes inhibition of translation of respective one or more VGAM527 host target proteins.

[23399] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM527 gene, herein designated VGAM GENE, on one or more VGAM527 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23400] It is yet further appreciated that a function of VGAM527 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,



utilities of VGAM527 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM527 correlate with, and may be deduced from, the identity of the host target genes which VGAM527 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23401] Nucleotide sequences of the VGAM527 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM527 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM527 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM527 are further described hereinbelow with reference to Table 1.

[23402] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM527 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM527 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23403] As mentioned hereinabove with reference to Fig. 1, a function of VGAM527 gene, herein designated VGAM is

inhibition of expression of VGAM527 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM527 correlate with, and may be deduced from, the identity of the target genes which VGAM527 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23404] BLAME (Accession NM\_020125) is a VGAM527 host target gene. BLAME BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BLAME, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLAME BINDING SITE, designated SEQ ID:21303, to the nucleotide sequence of VGAM527 RNA, herein designated VGAM RNA, also designated SEQ ID:3238.

[23405] A function of VGAM527 is therefore inhibition of BLAME (Accession NM\_020125). Accordingly, utilities of VGAM527 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLAME. LOC123242 (Accession XM\_063548) is another VGAM527 host target gene. LOC123242 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of

mRNA encoded by LOC123242, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC123242 BINDING SITE, designated SEQ ID:37240, to the nucleotide sequence of VGAM527 RNA, herein designated VGAM RNA, also designated SEQ ID:3238.

[23406] Another function of VGAM527 is therefore inhibition of LOC123242 (Accession XM\_063548). Accordingly, utilities of VGAM527 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC123242. LOC253001 (Accession XM\_171711) is another VGAM527 host target gene. LOC253001 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253001, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253001 BINDING SITE, designated SEQ ID:46057, to the nucleotide sequence of VGAM527 RNA, herein designated VGAM RNA, also designated SEQ ID:3238.

[23407] Another function of VGAM527 is therefore inhibition of LOC253001 (Accession XM\_171711). Accordingly, utilities

of VGAM527 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253001. LOC254413 (Accession XM\_173141) is another VGAM527 host target gene. LOC254413 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254413, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254413 BINDING SITE, designated SEQ ID:46403, to the nucleotide sequence of VGAM527 RNA, herein designated VGAM RNA, also designated SEQ ID:3238.

[23408] Another function of VGAM527 is therefore inhibition of LOC254413 (Accession XM\_173141). Accordingly, utilities of VGAM527 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254413. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 528 (VGAM528) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23409] VGAM528 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM528 was detected is described hereinabove with reference to Figs. 1–8.

[23410] VGAM528 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM528 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23411] VGAM528 gene encodes a VGAM528 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM528 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM528 precursor RNA is designated SEQ ID:514, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:514 is located at position 97660 relative to the genome of Murid Herpesvirus 4.

[23412] VGAM528 precursor RNA folds onto itself, forming VGAM528 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23413] An enzyme complex designated DICER COMPLEX, `dices` the VGAM528 folded precursor RNA into VGAM528 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 73%) nucleotide sequence of VGAM528 RNA is designated SEQ ID:3239, and is provided hereinbelow with reference to the sequence listing part.

[23414] VGAM528 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM528 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM528 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[23415] VGAM528 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM528 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM528 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM528 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM528 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23416] The complementary binding of VGAM528 RNA, herein designated VGAM RNA, to host target binding sites on VGAM528 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM528 host target RNA into VGAM528 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23417] It is appreciated that VGAM528 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM528 host target genes. The mRNA of each one of this plurality of VGAM528 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM528 RNA, herein designated VGAM RNA, and which when bound by VGAM528 RNA causes inhibition of translation of respective one or more VGAM528 host target proteins.

[23418] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM528 gene, herein designated VGAM GENE, on one or more VGAM528 host target gene, herein designated



VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23419] It is yet further appreciated that a function of VGAM528 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM528 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM528 correlate with, and may be deduced from, the identity of the host target genes which VGAM528 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23420] Nucleotide sequences of the VGAM528 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM528 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM528 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM528 are further  
described hereinbelow with reference to Table 1.

[23421] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM528 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM528 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[23422] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM528 gene, herein designated VGAM is  
inhibition of expression of VGAM528 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM528 correlate with, and may be deduced  
from, the identity of the target genes which VGAM528  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[23423] FAT Tumor Suppressor Homolog 1 (Drosophila) (FAT, Ac-  
cession NM\_005245) is a VGAM528 host target gene. FAT

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FAT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FAT BINDING SITE, designated SEQ ID:11753, to the nucleotide sequence of VGAM528 RNA, herein designated VGAM RNA, also designated SEQ ID:3239.

[23424] A function of VGAM528 is therefore inhibition of FAT Tumor Suppressor Homolog 1 (Drosophila) (FAT, Accession NM\_005245), a gene which possibly functions in developmental processes and cell communication. Accordingly, utilities of VGAM528 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FAT. The function of FAT has been established by previous studies. Cell-cell interactions that involve adhesion molecules are important in many developmental processes. Dunne et al. (1995) stated that many adhesion molecules have been found to be conserved between Drosophila and vertebrates, indicating that the adhesion molecules involved in tissue morphogenesis evolved long before the divergence of the arthropods and chordates Hortsch and Goodman, 1991). Adhesion molecules have

been classified into 4 major families: the immunoglobulin superfamily, the integrin superfamily, the selectin family, and the cadherin superfamily. Cadherins mediate homophilic, calcium-dependent cell-cell adhesion in a wide variety of tissues and are important regulators of morphogenesis, and loss of function may be involved in the invasion and metastasis of malignant tumors. The original or classical adherins have a highly conserved domain structure typically including 5 extracellular, conserved repeated amino acid sequences (cadherin repeats). The *Drosophila* 'fat' gene does not belong to the classical cadherin gene family yet encodes a transmembrane protein containing 34 cadherin repeats in association with a number of other motifs Mahoney et al. (1991). The *Drosophila* 'fat' locus encodes a tumor suppressor gene, and recessive (loss-of-function) mutations lead to hyperplastic overgrowth of the imaginal discs, indicating that contact-dependent cell interactions may play an important role in regulating growth (Bryant et al., 1988). This excessive cell proliferation occurs while maintaining normal epithelial organization and differentiation potential. Dunne et al. (1995) reported the sequence of a cDNA that was serendipitously obtained during a screen of a human T-

lymphocyte cDNA library. The full-length cDNA had the potential to encode a large protein that most resembled the *Drosophila* 'fat' protein in its possession of 34 cadherin repeats and other characteristics. Therefore, they named the gene and the gene product FAT. Analysis of the expression of FAT in fetal and adult tissues revealed that FAT mRNA is present in many epithelial and some endothelial and smooth muscle cells. The FAT gene was localized to 4q34-q35 by isotopic in situ hybridization. The authors commented that the molecule is probably important in mammalian developmental processes and cell communication. The large FAT protein was predicted to contain nearly 4600 residues

[23425] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23426] Hortsch, M.; Goodman, C. S. : Cell and substrate adhesion molecules in *Drosophila*. *Ann. Rev. Cell. Biol.* 7: 505-557, 1991. ; and

[23427] Mahoney, P. A.; Weber, U.; Onofrechuk, P.; Biessmann, H.; Bryant, P. J.; Goodman, C. S. : The fat tumor suppressor gene in *Drosophila* encodes a novel member of the cadherin gene superfa.

[23428] Further studies establishing the function and utilities of FAT are found in John Hopkins OMIM database record ID 600976, and in cited publications numbered 7800–7803 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Mitogen-activated Protein Kinase Kinase 1 (MAP2K1, Accession NM\_002755) is another VGAM528 host target gene. MAP2K1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAP2K1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP2K1 BINDING SITE, designated SEQ ID:8635, to the nucleotide sequence of VGAM528 RNA, herein designated VGAM RNA, also designated SEQ ID:3239.

[23429] Another function of VGAM528 is therefore inhibition of Mitogen-activated Protein Kinase Kinase 1 (MAP2K1, Accession NM\_002755), a gene which is a signaling intermediate, may take part in cell transformation. Accordingly, utilities of VGAM528 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP2K1. The function of MAP2K1 has been established by previous studies. Mitogen-activated protein

(MAP) kinases, also known as extracellular signal-regulated kinases (ERKs) (see OMIM Ref. No. PRKM1; 176948), are thought to act as an integration point for multiple biochemical signals because they are activated by a wide variety of extracellular signals, are rapidly phosphorylated on threonine and tyrosine residues, and are highly conserved in evolution (Crews et al., 1992). A critical protein kinase lies upstream of MAP kinase and stimulates the enzymatic activity of MAP kinase. Crews et al. (1992) cloned a mouse cDNA, denoted Mek1 (for Map/Erk kinase-1) by them, that encodes a member of this protein kinase family. The 393-amino acid, 43.5-kD protein is most closely related in size and sequence to the product encoded by the *byr1* gene of *S. pombe*. Crews et al. (1992) found that Mek1 protein expressed in bacteria phosphorylates the Erk gene product in vitro. They showed that the Mek1 gene is highly expressed in murine brain. Ryan et al. (2000) showed that inhibition of MEK1 blocks p53 (OMIM Ref. No. 191170)-induced NF-kappa-B activation and apoptosis but not cell cycle arrest. They demonstrated that p53 activates NF-kappa-B through the RAF/MEK1/p90(rsk) (see OMIM Ref. No. 601684) pathway rather than the TNFR1 (OMIM Ref. No. 191190)/TRAF2

(OMIM Ref. No. 601895)/IKK (e.g., 600664) pathway used by TNFA (OMIM Ref. No. 191160). To elucidate the mechanism through which MAPK signaling regulates the MYOD (OMIM Ref. No. 159970) family of transcription factors, Perry et al. (2001) investigated the role of the signaling intermediate MEK1 in myogenesis. Transfection of activated MEK1 strongly repressed gene activation and myogenic conversion by the MYOD family. This repression was not mediated by direct phosphorylation of MYOD or by changes in MYOD stability or subcellular distribution. Deletion mapping revealed that MEK1-mediated repression required the MYOD N-terminal transactivation domain. Moreover, activated MEK1 was nuclearly localized and bound a complex containing MYOD in a manner that was dependent on the presence of the MYOD N terminus. These data demonstrated that MEK1 signaling has a strong negative effect on MYOD activity via a mechanism involving binding of MEK1 to the nuclear MYOD transcriptional complex

[23430] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23431] Crews, C. M.; Alessandrini, A.; Erikson, R. L. : The primary



structure of MEK, a protein kinase that phosphorylates the ERK gene product. Science 258: 478–480, 1992. ; and

[23432] Perry, R. L. S.; Parker, M. H.; Rudnicki, M. A. : Activated MEK1 binds the nuclear MyoD transcriptional complex to repress transactivation. Molec. Cell 8: 291–301, 2001.

[23433] Further studies establishing the function and utilities of MAP2K1 are found in John Hopkins OMIM database record ID 176872, and in cited publications numbered 10344–10356 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0561 (Accession XM\_038150) is another VGAM528 host target gene. KIAA0561 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0561, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0561 BINDING SITE, designated SEQ ID:32767, to the nucleotide sequence of VGAM528 RNA, herein designated VGAM RNA, also designated SEQ ID:3239.

[23434] Another function of VGAM528 is therefore inhibition of KIAA0561 (Accession XM\_038150). Accordingly, utilities of VGAM528 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0561. LOC120105 (Accession XM\_061864) is another VGAM528 host target gene. LOC120105 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC120105, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120105 BINDING SITE, designated SEQ ID:37209, to the nucleotide sequence of VGAM528 RNA, herein designated VGAM RNA, also designated SEQ ID:3239.

[23435] Another function of VGAM528 is therefore inhibition of LOC120105 (Accession XM\_061864). Accordingly, utilities of VGAM528 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120105. LOC129831 (Accession XM\_059376) is another VGAM528 host target gene. LOC129831 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC129831, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC129831 BINDING SITE, designated SEQ ID:36978, to

the nucleotide sequence of VGAM528 RNA, herein designated VGAM RNA, also designated SEQ ID:3239.

[23436] Another function of VGAM528 is therefore inhibition of LOC129831 (Accession XM\_059376). Accordingly, utilities of VGAM528 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129831. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 529 (VGAM529) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23437] VGAM529 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM529 was detected is described hereinabove with reference to Figs. 1–8.

[23438] VGAM529 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM529 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23439] VGAM529 gene encodes a VGAM529 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM529 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM529 precursor RNA is designated SEQ ID:515, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:515 is located at position 102688 relative to the genome of Murid Herpesvirus 4.

[23440] VGAM529 precursor RNA folds onto itself, forming VGAM529 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23441] An enzyme complex designated DICER COMPLEX, `dices` the VGAM529 folded precursor RNA into VGAM529 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM529 RNA is designated SEQ ID:3240, and is provided hereinbelow with reference to the sequence listing part.

[23442] VGAM529 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM529 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM529 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[23443] VGAM529 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM529 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM529 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM529 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM529 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23444] The complementary binding of VGAM529 RNA, herein designated VGAM RNA, to host target binding sites on VGAM529 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM529 host target RNA into VGAM529 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23445] It is appreciated that VGAM529 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM529 host target genes. The mRNA of each one of this plurality of VGAM529 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM529 RNA, herein designated VGAM RNA, and which when bound by VGAM529 RNA causes inhibition of translation of respective one or more VGAM529 host target proteins.

[23446] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM529 gene, herein designated VGAM GENE, on one or more VGAM529 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[23447] It is yet further appreciated that a function of VGAM529 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM529 correlate with, and may be deduced from, the identity of the host target genes which VGAM529 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23448] Nucleotide sequences of the VGAM529 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM529 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM529 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM529 are further described hereinbelow with reference to Table 1.

[23449] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM529 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM529 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23450] As mentioned hereinabove with reference to Fig. 1, a function of VGAM529 gene, herein designated VGAM is inhibition of expression of VGAM529 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM529 correlate with, and may be deduced from, the identity of the target genes which VGAM529 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23451] DNA Fragmentation Factor, 40kDa, Beta Polypeptide (caspase-activated DNase) (DFFB, Accession XM\_113366) is a VGAM529 host target gene. DFFB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DFFB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DFFB BINDING SITE, designated SEQ ID:42243, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23452] A function of VGAM529 is therefore inhibition of DNA

Fragmentation Factor, 40kDa, Beta Polypeptide (caspase-activated DNase) (DFFB, Accession XM\_113366), a gene which induces DNA fragmentation and chromatin condensation during apoptosis. Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DFFB. The function of DFFB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74.

Fibroblast Growth Factor 5 (FGF5, Accession NM\_004464) is another VGAM529 host target gene. FGF5 BINDING SITE1 and FGF5 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGF5, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF5 BINDING SITE1 and FGF5 BINDING SITE2, designated SEQ ID:10774 and SEQ ID:27001 respectively, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23453] Another function of VGAM529 is therefore inhibition of Fibroblast Growth Factor 5 (FGF5, Accession NM\_004464), a gene which induces transformation and may regulate neuronal differentiation. Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF5. The function of FGF5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM276. Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3, Accession NM\_004273) is another VGAM529 host target gene. CHST3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHST3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST3 BINDING SITE, designated SEQ ID:10485, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23454] Another function of VGAM529 is therefore inhibition of Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3, Accession NM\_004273). Accordingly, utilities of VGAM529

include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHST3. FLJ10713 (Accession NM\_018189) is another VGAM529 host target gene. FLJ10713 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10713, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10713 BINDING SITE, designated SEQ ID:20041, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23455] Another function of VGAM529 is therefore inhibition of FLJ10713 (Accession NM\_018189). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10713. FLJ12363 (Accession NM\_032167) is another VGAM529 host target gene. FLJ12363 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12363, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12363 BINDING SITE,

designated SEQ ID:25867, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23456] Another function of VGAM529 is therefore inhibition of FLJ12363 (Accession NM\_032167). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12363. FLJ12973 (Accession NM\_024908) is another VGAM529 host target gene. FLJ12973 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12973, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12973 BINDING SITE, designated SEQ ID:24407, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23457] Another function of VGAM529 is therefore inhibition of FLJ12973 (Accession NM\_024908). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12973. FLJ22684 (Accession NM\_025048) is another VGAM529 host target gene. FLJ22684 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ22684, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22684 BINDING SITE, designated SEQ ID:24643, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23458] Another function of VGAM529 is therefore inhibition of FLJ22684 (Accession NM\_025048). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22684. FLJ31101 (Accession NM\_017964) is another VGAM529 host target gene. FLJ31101 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ31101, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ31101 BINDING SITE, designated SEQ ID:19684, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23459] Another function of VGAM529 is therefore inhibition of

FLJ31101 (Accession NM\_017964). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ31101. KIAA0513 (Accession NM\_014732) is another VGAM529 host target gene. KIAA0513 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0513, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0513 BINDING SITE, designated SEQ ID:16357, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23460] Another function of VGAM529 is therefore inhibition of KIAA0513 (Accession NM\_014732). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0513. MDS018 (Accession NM\_021823) is another VGAM529 host target gene. MDS018 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MDS018, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of MDS018 BINDING SITE, designated SEQ ID:22402, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23461] Another function of VGAM529 is therefore inhibition of MDS018 (Accession NM\_021823). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MDS018. MGC11386 (Accession NM\_032933) is another VGAM529 host target gene. MGC11386 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC11386, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC11386 BINDING SITE, designated SEQ ID:26756, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23462] Another function of VGAM529 is therefore inhibition of MGC11386 (Accession NM\_032933). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC11386. MGC15416 (Accession NM\_138418) is an-



other VGAM529 host target gene. MGC15416 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC15416, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15416 BINDING SITE, designated SEQ ID:28788, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23463] Another function of VGAM529 is therefore inhibition of MGC15416 (Accession NM\_138418). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15416. MGC2474 (Accession NM\_023931) is another VGAM529 host target gene. MGC2474 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC2474, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2474 BINDING SITE, designated SEQ ID:23417, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23464] Another function of VGAM529 is therefore inhibition of MGC2474 (Accession NM\_023931). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2474. PRO2389 (Accession XM\_033334) is another VGAM529 host target gene. PRO2389 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRO2389, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2389 BINDING SITE, designated SEQ ID:31880, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23465] Another function of VGAM529 is therefore inhibition of PRO2389 (Accession XM\_033334). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2389. Protein Tyrosine Phosphatase, Receptor Type, N Polypeptide 2 (PTPRN2, Accession NM\_130842) is another VGAM529 host target gene. PTPRN2 BINDING SITE1 and PTPRN2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PT-

PRN2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPRN2 BINDING SITE1 and PTPRN2 BINDING SITE2, designated SEQ ID:28371 and SEQ ID:28376 respectively, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23466] Another function of VGAM529 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, N Polypeptide 2 (PTPRN2, Accession NM\_130842). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRN2. LOC146909 (Accession XM\_085634) is another VGAM529 host target gene. LOC146909 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146909, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146909 BINDING SITE, designated SEQ ID:38267, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23467] Another function of VGAM529 is therefore inhibition of LOC146909 (Accession XM\_085634). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146909. LOC152313 (Accession XM\_098190) is another VGAM529 host target gene. LOC152313 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152313, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152313 BINDING SITE, designated SEQ ID:41476, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23468] Another function of VGAM529 is therefore inhibition of LOC152313 (Accession XM\_098190). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152313. LOC154877 (Accession XM\_098626) is another VGAM529 host target gene. LOC154877 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154877, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154877 BINDING SITE, designated SEQ ID:41742, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23469] Another function of VGAM529 is therefore inhibition of LOC154877 (Accession XM\_098626). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154877. LOC169026 (Accession XM\_095471) is another VGAM529 host target gene. LOC169026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC169026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169026 BINDING SITE, designated SEQ ID:40265, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23470] Another function of VGAM529 is therefore inhibition of LOC169026 (Accession XM\_095471). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC169026. LOC200014 (Accession XM\_114087) is another VGAM529 host target gene. LOC200014 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200014 BINDING SITE, designated SEQ ID:42691, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23471] Another function of VGAM529 is therefore inhibition of LOC200014 (Accession XM\_114087). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200014. LOC254439 (Accession XM\_170659) is another VGAM529 host target gene. LOC254439 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254439, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254439 BINDING SITE, designated SEQ ID:45432, to the nucleotide sequence of VGAM529 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3240.

[23472] Another function of VGAM529 is therefore inhibition of LOC254439 (Accession XM\_170659). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254439. LOC57107 (Accession NM\_020381) is another VGAM529 host target gene. LOC57107 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC57107, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57107 BINDING SITE, designated SEQ ID:21649, to the nucleotide sequence of VGAM529 RNA, herein designated VGAM RNA, also designated SEQ ID:3240.

[23473] Another function of VGAM529 is therefore inhibition of LOC57107 (Accession NM\_020381). Accordingly, utilities of VGAM529 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57107. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 530 (VGAM530) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23474] VGAM530 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM530 was detected is described hereinabove with reference to Figs. 1–8.

[23475] VGAM530 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Common Chimpanzee Papillomavirus 1. VGAM530 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23476] VGAM530 gene encodes a VGAM530 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM530 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM530 precursor RNA is designated SEQ ID:516, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:516 is located at position 2882 relative to the genome of Common Chimpanzee Papillomavirus 1.

[23477] VGAM530 precursor RNA folds onto itself, forming



VGAM530 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23478] An enzyme complex designated DICER COMPLEX, `dices` the VGAM530 folded precursor RNA into VGAM530 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 78%) nucleotide sequence of VGAM530 RNA is designated SEQ ID:3241, and is provided hereinbelow with reference to the sequence listing part.

[23479] VGAM530 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM530 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM530 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23480] VGAM530 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM530 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM530 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM530 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM530 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23481] The complementary binding of VGAM530 RNA, herein designated VGAM RNA, to host target binding sites on VGAM530 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM530 host target RNA into VGAM530 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23482] It is appreciated that VGAM530 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM530 host target genes. The mRNA of each one of this plurality of VGAM530 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM530 RNA, herein designated VGAM RNA, and which when bound by VGAM530 RNA causes inhibition of translation of respective one or more VGAM530 host target proteins.

[23483] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM530 gene, herein designated VGAM GENE, on one or more VGAM530 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23484] It is yet further appreciated that a function of VGAM530 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of viral infection by Common Chimpanzee Papillomavirus 1. Specific functions, and accordingly utilities, of VGAM530 correlate with, and may be deduced from, the identity of the host target genes which

VGAM530 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23485] Nucleotide sequences of the VGAM530 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM530 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM530 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM530 are further described hereinbelow with reference to Table 1.

[23486] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM530 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM530 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23487] As mentioned hereinabove with reference to Fig. 1, a function of VGAM530 gene, herein designated VGAM is inhibition of expression of VGAM530 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM530 correlate with, and may be deduced from, the identity of the target genes which VGAM530 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[23488] 5'-nucleotidase, Cytosolic II (NT5C2, Accession NM\_012229) is a VGAM530 host target gene. NT5C2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NT5C2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NT5C2 BINDING SITE, designated SEQ ID:14527, to the nucleotide sequence of VGAM530 RNA, herein designated VGAM RNA, also designated SEQ ID:3241.

[23489] A function of VGAM530 is therefore inhibition of 5'-nucleotidase, Cytosolic II (NT5C2, Accession NM\_012229). Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NT5C2. Rho-associated, Coiled-coil Containing Protein Kinase 2 (ROCK2, Accession XM\_038377) is another VGAM530 host target gene. ROCK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ROCK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of ROCK2 BINDING SITE, designated SEQ ID:32838, to the nucleotide sequence of VGAM530 RNA, herein designated VGAM RNA, also designated SEQ ID:3241.

[23490] Another function of VGAM530 is therefore inhibition of Rho-associated, Coiled-coil Containing Protein Kinase 2 (ROCK2, Accession XM\_038377), a gene which regulates cytokinesis, smooth muscle contraction, the formation of actin stress fibers and focal adhesions. Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ROCK2. The function of ROCK2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM273.FLJ13852 (Accession NM\_023078) is another VGAM530 host target gene. FLJ13852 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13852, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13852 BINDING SITE, designated SEQ ID:23339, to the nucleotide sequence of VGAM530 RNA, herein designated

VGAM RNA, also designated SEQ ID:3241.

[23491] Another function of VGAM530 is therefore inhibition of FLJ13852 (Accession NM\_023078). Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13852. FLJ23563 (Accession XM\_041701) is another VGAM530 host target gene. FLJ23563 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ23563, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23563 BINDING SITE, designated SEQ ID:33561, to the nucleotide sequence of VGAM530 RNA, herein designated VGAM RNA, also designated SEQ ID:3241.

[23492] Another function of VGAM530 is therefore inhibition of FLJ23563 (Accession XM\_041701). Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23563. KIAA0161 (Accession NM\_014746) is another VGAM530 host target gene. KIAA0161 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0161, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0161 BINDING SITE, designated SEQ ID:16430, to the nucleotide sequence of VGAM530 RNA, herein designated VGAM RNA, also designated SEQ ID:3241.

[23493] Another function of VGAM530 is therefore inhibition of KIAA0161 (Accession NM\_014746). Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0161. LanC Lantibiotic Synthetase Component C-like 2 (bacterial) (LANCL2, Accession NM\_018697) is another VGAM530 host target gene. LANCL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LANCL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LANCL2 BINDING SITE, designated SEQ ID:20775, to the nucleotide sequence of VGAM530 RNA, herein designated VGAM RNA, also designated SEQ ID:3241.

[23494] Another function of VGAM530 is therefore inhibition of LanC Lantibiotic Synthetase Component C-like 2

(bacterial) (LANCL2, Accession NM\_018697). Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LANCL2. MAP (Accession NM\_022818) is another VGAM530 host target gene. MAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP BINDING SITE, designated SEQ ID:23095, to the nucleotide sequence of VGAM530 RNA, herein designated VGAM RNA, also designated SEQ ID:3241.

[23495] Another function of VGAM530 is therefore inhibition of MAP (Accession NM\_022818). Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP. LOC221421 (Accession XM\_166428) is another VGAM530 host target gene. LOC221421 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221421, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of LOC221421 BINDING SITE, designated SEQ ID:44322, to the nucleotide sequence of VGAM530 RNA, herein designated VGAM RNA, also designated SEQ ID:3241.

[23496] Another function of VGAM530 is therefore inhibition of LOC221421 (Accession XM\_166428). Accordingly, utilities of VGAM530 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221421. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 531 (VGAM531) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23497] VGAM531 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM531 was detected is described hereinabove with reference to Figs. 1–8.

[23498] VGAM531 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 4. VGAM531 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[23499] VGAM531 gene encodes a VGAM531 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM531 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM531 precursor RNA is designated SEQ ID:517, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:517 is located at position 130187 relative to the genome of Equine Herpesvirus 4.

[23500] VGAM531 precursor RNA folds onto itself, forming VGAM531 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23501] An enzyme complex designated DICER COMPLEX, `dices` the VGAM531 folded precursor RNA into VGAM531 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM531 RNA is designated SEQ ID:3242, and is provided hereinbelow with reference to the sequence listing part.

[23502] VGAM531 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM531 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM531 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23503] VGAM531 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM531 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM531 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM531 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM531 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23504] The complementary binding of VGAM531 RNA, herein designated VGAM RNA, to host target binding sites on VGAM531 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM531 host target RNA into VGAM531 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23505] It is appreciated that VGAM531 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM531 host target genes. The mRNA of each one of this plurality of VGAM531 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM531 RNA, herein designated VGAM RNA, and which when bound by VGAM531 RNA causes inhibition of translation of respective one or more VGAM531 host target proteins.

[23506] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM531 gene, herein designated VGAM GENE, on one or more VGAM531 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23507] It is yet further appreciated that a function of VGAM531 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM531 correlate with, and may be deduced from, the identity of the host target genes which VGAM531 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23508] Nucleotide sequences of the VGAM531 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM531 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM531 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM531 are further described hereinbelow with reference to Table 1.

[23509] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of



Fig. 1, found on VGAM531 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM531 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23510] As mentioned hereinabove with reference to Fig. 1, a function of VGAM531 gene, herein designated VGAM is inhibition of expression of VGAM531 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM531 correlate with, and may be deduced from, the identity of the target genes which VGAM531 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23511] Potassium Voltage-gated Channel, Delayed-rectifier, Sub-family S, Member 3 (KCNS3, Accession NM\_002252) is a VGAM531 host target gene. KCNS3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KCNS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNS3 BINDING SITE, designated SEQ ID:8050, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3242.

[23512] A function of VGAM531 is therefore inhibition of Potassium Voltage-gated Channel, Delayed-rectifier, Subfamily S, Member 3 (KCNS3, Accession NM\_002252). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNS3. Myotubularin Related Protein 2 (MTMR2, Accession NM\_016156) is another VGAM531 host target gene. MTMR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MTMR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTMR2 BINDING SITE, designated SEQ ID:18246, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23513] Another function of VGAM531 is therefore inhibition of Myotubularin Related Protein 2 (MTMR2, Accession NM\_016156). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTMR2. FLJ10052 (Accession NM\_017982) is another VGAM531 host target

gene. FLJ10052 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10052, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10052 BINDING SITE, designated SEQ ID:19712, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23514] Another function of VGAM531 is therefore inhibition of FLJ10052 (Accession NM\_017982). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10052. G4 (Accession XM\_165712) is another VGAM531 host target gene. G4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by G4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of G4 BINDING SITE, designated SEQ ID:43736, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23515] Another function of VGAM531 is therefore inhibition of G4

(Accession XM\_165712). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with G4.

KIAA1246 (Accession XM\_166372) is another VGAM531 host target gene. KIAA1246 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1246, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1246 BINDING SITE, designated SEQ ID:44193, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23516] Another function of VGAM531 is therefore inhibition of KIAA1246 (Accession XM\_166372). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1246. RALGPS1A (Accession NM\_014636) is another VGAM531 host target gene. RALGPS1A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RALGPS1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of RALGPS1A BINDING SITE, designated SEQ ID:16019, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23517] Another function of VGAM531 is therefore inhibition of RALGPS1A (Accession NM\_014636). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RALGPS1A. LOC158337 (Accession XM\_098926) is another VGAM531 host target gene. LOC158337 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158337 BINDING SITE, designated SEQ ID:41961, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23518] Another function of VGAM531 is therefore inhibition of LOC158337 (Accession XM\_098926). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158337. LOC200261 (Accession XM\_114172) is an-

other VGAM531 host target gene. LOC200261 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200261 BINDING SITE, designated SEQ ID:42752, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23519] Another function of VGAM531 is therefore inhibition of LOC200261 (Accession XM\_114172). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200261. LOC203292 (Accession XM\_117527) is another VGAM531 host target gene. LOC203292 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC203292, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203292 BINDING SITE, designated SEQ ID:43503, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23520] Another function of VGAM531 is therefore inhibition of LOC203292 (Accession XM\_117527). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203292. LOC219744 (Accession XM\_166123) is another VGAM531 host target gene. LOC219744 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219744, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219744 BINDING SITE, designated SEQ ID:43903, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23521] Another function of VGAM531 is therefore inhibition of LOC219744 (Accession XM\_166123). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219744. LOC221479 (Accession XM\_166417) is another VGAM531 host target gene. LOC221479 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221479, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221479 BINDING SITE, designated SEQ ID:44289, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23522] Another function of VGAM531 is therefore inhibition of LOC221479 (Accession XM\_166417). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221479. LOC257554 (Accession XM\_175149) is another VGAM531 host target gene. LOC257554 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257554, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257554 BINDING SITE, designated SEQ ID:46643, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23523] Another function of VGAM531 is therefore inhibition of LOC257554 (Accession XM\_175149). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC257554. LOC92973 (Accession XM\_048529) is another VGAM531 host target gene. LOC92973 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92973, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92973 BINDING SITE, designated SEQ ID:35188, to the nucleotide sequence of VGAM531 RNA, herein designated VGAM RNA, also designated SEQ ID:3242.

[23524] Another function of VGAM531 is therefore inhibition of LOC92973 (Accession XM\_048529). Accordingly, utilities of VGAM531 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92973. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 532 (VGAM532) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23525] VGAM532 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM532 was detected is described hereinabove with reference to Figs. 1–8.

[23526] VGAM532 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murine Hepatitis Virus. VGAM532 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23527] VGAM532 gene encodes a VGAM532 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM532 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM532 precursor RNA is designated SEQ ID:518, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:518 is located at position 27967 relative to the genome of Murine Hepatitis Virus.

[23528] VGAM532 precursor RNA folds onto itself, forming VGAM532 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23529] An enzyme complex designated DICER COMPLEX, `dices` the VGAM532 folded precursor RNA into VGAM532 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 70%) nucleotide sequence of VGAM532 RNA is designated SEQ ID:3243, and is provided hereinbelow with reference to the sequence listing part.

[23530] VGAM532 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM532 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM532 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23531] VGAM532 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM532 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM532 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM532 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM532 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23532] The complementary binding of VGAM532 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM532 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM532 host target RNA into VGAM532 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23533] It is appreciated that VGAM532 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM532 host target genes. The mRNA of each one of this plurality of VGAM532 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM532 RNA, herein designated VGAM RNA, and which when bound by VGAM532 RNA causes inhibition of translation of respective one or more VGAM532 host target proteins.

[23534] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM532 gene, herein designated VGAM GENE, on one or more VGAM532 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23535] It is yet further appreciated that a function of VGAM532 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of viral infection by Murine Hepatitis Virus. Specific functions, and accordingly utilities, of VGAM532 correlate with, and may be deduced from, the identity of the host target genes which VGAM532 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23536] Nucleotide sequences of the VGAM532 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM532 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM532 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM532 are further described hereinbelow with reference to Table 1.

[23537] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM532 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM532 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23538] As mentioned hereinabove with reference to Fig. 1, a function of VGAM532 gene, herein designated VGAM is inhibition of expression of VGAM532 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM532 correlate with, and may be deduced from, the identity of the target genes which VGAM532 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23539] Chemokine-like Receptor 1 (CMKLR1, Accession NM\_004072) is a VGAM532 host target gene. CMKLR1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CMKLR1,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CMKLR1 BINDING SITE, designated SEQ ID:10275, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23540] A function of VGAM532 is therefore inhibition of Chemokine-like Receptor 1 (CMKLR1, Accession NM\_004072), a gene which may have a function in bone metabolism. Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CMKLR1. The function of CMKLR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM237.LENG4 (Accession NM\_024298) is another VGAM532 host target gene. LENG4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LENG4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LENG4 BINDING SITE,



designated SEQ ID:23579, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23541] Another function of VGAM532 is therefore inhibition of LENG4 (Accession NM\_024298), a gene which may be a transmembrane protein. Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LENG4. The function of LENG4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM259. Low Density Lipoprotein Receptor-related Protein 4 (LRP4, Accession XM\_035037) is another VGAM532 host target gene. LRP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LRP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRP4 BINDING SITE, designated SEQ ID:32194, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23542] Another function of VGAM532 is therefore inhibition of

Low Density Lipoprotein Receptor-related Protein 4 (LRP4, Accession XM\_035037). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRP4. SRY (sex determining region Y)-box 10 (SOX10, Accession NM\_006941) is another VGAM532 host target gene. SOX10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SOX10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOX10 BINDING SITE, designated SEQ ID:13826, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23543] Another function of VGAM532 is therefore inhibition of SRY (sex determining region Y)-box 10 (SOX10, Accession NM\_006941). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOX10. Fidgetin (FIGN, Accession XM\_171005) is another VGAM532 host target gene. FIGN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

FIGN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FIGN BINDING SITE, designated SEQ ID:45777, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23544] Another function of VGAM532 is therefore inhibition of Fidgetin (FIGN, Accession XM\_171005). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FIGN. KIAA0759 (Accession XM\_041090) is another VGAM532 host target gene. KIAA0759 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0759, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0759 BINDING SITE, designated SEQ ID:33441, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23545] Another function of VGAM532 is therefore inhibition of KIAA0759 (Accession XM\_041090). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0759. KIAA1058 (Accession XM\_090586) is another VGAM532 host target gene. KIAA1058 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1058, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1058 BINDING SITE, designated SEQ ID:40012, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23546] Another function of VGAM532 is therefore inhibition of KIAA1058 (Accession XM\_090586). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1058. Sorting Nexin 10 (SNX10, Accession NM\_013322) is another VGAM532 host target gene. SNX10 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SNX10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNX10 BINDING SITE, designated SEQ

ID:14968, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23547] Another function of VGAM532 is therefore inhibition of Sorting Nexin 10 (SNX10, Accession NM\_013322). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNX10. LOC146714 (Accession XM\_097072) is another VGAM532 host target gene. LOC146714 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146714, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146714 BINDING SITE, designated SEQ ID:40722, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23548] Another function of VGAM532 is therefore inhibition of LOC146714 (Accession XM\_097072). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146714. LOC150142 (Accession XM\_086791) is another VGAM532 host target gene. LOC150142 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC150142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150142 BINDING SITE, designated SEQ ID:38854, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23549] Another function of VGAM532 is therefore inhibition of LOC150142 (Accession XM\_086791). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150142. LOC150696 (Accession NM\_144707) is another VGAM532 host target gene. LOC150696 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC150696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150696 BINDING SITE, designated SEQ ID:29531, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23550] Another function of VGAM532 is therefore inhibition of

LOC150696 (Accession NM\_144707). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150696. LOC220980 (Accession XM\_167629) is another VGAM532 host target gene. LOC220980 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220980, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220980 BINDING SITE, designated SEQ ID:44738, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23551] Another function of VGAM532 is therefore inhibition of LOC220980 (Accession XM\_167629). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220980. LOC92539 (Accession XM\_045632) is another VGAM532 host target gene. LOC92539 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92539, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of LOC92539 BINDING SITE, designated SEQ ID:34504, to the nucleotide sequence of VGAM532 RNA, herein designated VGAM RNA, also designated SEQ ID:3243.

[23552] Another function of VGAM532 is therefore inhibition of LOC92539 (Accession XM\_045632). Accordingly, utilities of VGAM532 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92539. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 533 (VGAM533) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23553] VGAM533 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM533 was detected is described hereinabove with reference to Figs. 1–8.

[23554] VGAM533 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turnip Vein-clearing Virus. VGAM533 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in



the human genome.

[23555] VGAM533 gene encodes a VGAM533 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM533 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM533 precursor RNA is designated SEQ ID:519, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:519 is located at position 4883 relative to the genome of Turnip Vein-clearing Virus.

[23556] VGAM533 precursor RNA folds onto itself, forming VGAM533 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23557] An enzyme complex designated DICER COMPLEX, `dices` the VGAM533 folded precursor RNA into VGAM533 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM533 RNA is designated SEQ ID:3244, and is provided hereinbelow with reference to the sequence listing part.

[23558] VGAM533 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM533 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM533 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23559] VGAM533 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM533 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM533 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM533 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM533 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23560] The complementary binding of VGAM533 RNA, herein designated VGAM RNA, to host target binding sites on VGAM533 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM533 host target RNA into VGAM533 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23561] It is appreciated that VGAM533 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM533 host target genes. The mRNA of each one of this plurality of VGAM533 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM533 RNA, herein designated VGAM RNA, and which when bound by VGAM533 RNA causes inhibition of translation of respective one or more VGAM533 host target proteins.

[23562] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM533 gene, herein designated VGAM GENE, on one or more VGAM533 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23563] It is yet further appreciated that a function of VGAM533 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of viral infection by Turnip Vein-clearing Virus. Specific functions, and accordingly utilities, of VGAM533 correlate with, and may be deduced from, the identity of the host target genes which VGAM533 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23564] Nucleotide sequences of the VGAM533 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM533 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM533 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM533 are further described hereinbelow with reference to Table 1.

[23565] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM533 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM533 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23566] As mentioned hereinabove with reference to Fig. 1, a function of VGAM533 gene, herein designated VGAM is inhibition of expression of VGAM533 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM533 correlate with, and may be deduced from, the identity of the target genes which VGAM533 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23567] A Kinase (PRKA) Anchor Protein 13 (AKAP13, Accession XM\_116974) is a VGAM533 host target gene. AKAP13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKAP13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP13 BINDING SITE, designated SEQ ID:43176, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23568] A function of VGAM533 is therefore inhibition of A Kinase (PRKA) Anchor Protein 13 (AKAP13, Accession XM\_116974), a gene which regulates subcellular localization of type II cAMP-dependent PKA. Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP13. The function of AKAP13 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM17.BTB and CNC Homology 1, Basic Leucine Zipper Transcription Factor 2 (BACH2, Accession NM\_021813) is another VGAM533 host target gene. BACH2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BACH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACH2 BINDING SITE, designated SEQ ID:22376, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23569] Another function of VGAM533 is therefore inhibition of BTB and CNC Homology 1, Basic Leucine Zipper Transcrip-

tion Factor 2 (BACH2, Accession NM\_021813), a gene which acts as repressor or activator, binds to maf recognition elements. Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACH2. The function of BACH2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM331. Cannabinoid Receptor 1 (brain) (CNR1, Accession NM\_016083) is another VGAM533 host target gene. CNR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNR1 BINDING SITE, designated SEQ ID:18165, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23570] Another function of VGAM533 is therefore inhibition of Cannabinoid Receptor 1 (brain) (CNR1, Accession NM\_016083), a gene which is involved in the cannabinoid-induced CNS effects. Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with CNR1. The function of CNR1 has been established by previous studies. Ledent et al. (1999) investigated the function of the central cannabinoid receptor (CB1) by disrupting the gene in mice. Mutant mice did not respond to cannabinoid drugs, demonstrating the exclusive role of CB1 in mediating analgesia, reinforcement, hypothermia, hypolocomotion, and hypotension. The acute effects of opiates were unaffected, but the reinforcing properties of morphine and the severity of the withdrawal syndrome were strongly reduced. These observations suggested that CB1 is involved in the motivational properties of opiates and in the development of physical dependence, and extended the concept of an interconnected role of CB1 and opiate receptors in the brain areas mediating addictive behavior. The cannabinoids are psychoactive ingredients of marijuana, principally delta-9-tetrahydrocannabinol, as well as the synthetic analogs. Matsuda et al. (1990) cloned a cannabinoid receptor from a rat brain. Gerard et al. (1991) isolated a cDNA encoding a cannabinoid receptor from a human brain stem cDNA library. The deduced amino acid sequence encoded a protein of 472 residues which shared 97.3% identity with the rat cannabinoid receptor cloned by

Matsuda et al. (1990). They provided evidence for the existence of an identical cannabinoid receptor expressed in human testis. Animal model experiments lend further support to the function of CNR1. Di Marzo et al. (2001) showed that following temporary food restriction, CB1 receptor knockout mice eat less than their wildtype littermates, and the CB1 antagonist SR141716A reduces food intake in wildtype but not knockout mice. Furthermore, defective leptin (OMIM Ref. No. 164160) signaling is associated with elevated hypothalamic, but not cerebellar, levels of endocannabinoids in obese db/db and ob/ob mice and Zucker rats. Acute leptin treatment of normal rats and ob/ob mice reduces anandamide and 2-arachidonoyl glycerol in the hypothalamus. Di Marzo et al. (2001) concluded that endocannabinoids in the hypothalamus may tonically activate CB1 receptors to maintain food intake and form part of the neural circuitry regulated by leptin.

[23571] It is appreciated that the abovementioned animal model for CNR1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[23572] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [23573] Ledent, C.; Valverde, O.; Cossu, G.; Petitet, F.; Aubert, J.-F.; Beslot, F.; Bohme, G. A.; Imperato, A.; Pedrazzini, T.; Roques, B. P.; Vassart, G.; Fratta, W.; Parmentier, M. : Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CB(1) receptor knockout mice. *Science* 283: :401–404, 1999. ; and
- [23574] Gerard, C. M.; Mollereau, C.; Vassart, G.; Parmentier, M. : Molecular cloning of a human cannabinoid receptor which is also expressed in testis. *Biochem. J.* 279: 129–134, 1991.
- [23575] Further studies establishing the function and utilities of CNR1 are found in John Hopkins OMIM database record ID 114610, and in cited publications numbered 3702–3709 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DEAD/H (Asp–Glu–Ala–Asp/His) Box Polypeptide 6 (RNA helicase, 54kDa) (DDX6, Accession NM\_004397) is another VGAM533 host target gene. DDX6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DDX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen–

tarity of the nucleotide sequences of DDX6 BINDING SITE, designated SEQ ID:10641, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23576] Another function of VGAM533 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 6 (RNA helicase, 54kDa) (DDX6, Accession NM\_004397), a gene which is putative RNA helicases. Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDX6. The function of DDX6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179.Discs, Large (Drosophila) Homolog 5 (DLG5, Accession XM\_096398) is another VGAM533 host target gene. DLG5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DLG5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLG5 BINDING SITE, designated SEQ ID:40332, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23577] Another function of VGAM533 is therefore inhibition of Discs, Large (Drosophila) Homolog 5 (DLG5, Accession XM\_096398), a gene which may transmit extracellular signals to inhibit cell proliferation. Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLG5. The function of DLG5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM444. EphB2 (EPHB2, Accession NM\_004442) is another VGAM533 host target gene. EPHB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPHB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPHB2 BINDING SITE, designated SEQ ID:10731, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23578] Another function of VGAM533 is therefore inhibition of EphB2 (EPHB2, Accession NM\_004442), a gene which Eph-related receptor tyrosine kinase B2; may have a role in neurogenesis. Accordingly, utilities of VGAM533 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with EPHB2. The function of EPHB2 has been established by previous studies. See 179610 for background on Eph receptors and their ligands, the ephrins. Chan and Watt (1991) cloned partial sequences of the EEK (EPHA8; 176945) and ERK genes encoding members of the EPH subclass of receptor protein-tyrosine kinases. Northern blot analysis of rat RNA showed that DNA encoding human ERK hybridized to transcripts most abundantly in lung. By screening a human fetal brain cDNA expression library using a monoclonal antiphosphotyrosine antibody and by 5-prime RACE (rapid amplification of cDNA ends) procedures, Ikegaki et al. (1995) isolated overlapping cDNAs encoding a receptor-type tyrosine kinase belonging to the EPH family and designated the gene DRT (for developmentally regulated EPH-related tyrosine kinase). The DRT gene is expressed in transcripts of 3 different sizes (4, 5, and 11 kb). The DRT transcripts are expressed in human brain and several other tissues, including heart, lung, kidney, placenta, pancreas, liver, and skeletal muscle, but the 11-kb DRT transcript is preferentially expressed in fetal brain. Steady-state levels of DRT mRNA in several tissues, including brain, heart, lung,

and kidney, are greater in the midterm fetus than those in the adult. Ikegaki et al. (1995) showed that a large number of tumor cell lines derived from neuroectoderm express DRT transcripts. The authors speculated that DRT may play a part in human neurogenesis. Using a yeast 2-hybrid system, Cowan et al. (2000) demonstrated that PDZ domain-containing protein Pick1 (PRKCABP; 605926) binds the C-terminal tail of EphB2. Using colocalization studies and biochemical analysis, they demonstrated that a protein complex containing EphB2 and aquaporin-1 (AQP1; 107776) is formed in vivo. They concluded that Ephb2 may regulate ionic homeostasis and endolymph fluid production through macromolecular associations with membrane channels that transport chloride, bicarbonate, and water. Chan and Watt (1991) mapped the EEK and ERK genes to chromosome 1 by Southern blot analysis of somatic cell hybrids. Ikegaki et al. (1995) mapped DRT, the EPHB2 gene, to 1p36.1-p35 by PCR screening of human/rodent somatic cell hybrid panels and by fluorescence in situ hybridization. As the distal end of 1p is often deleted in neuroblastomas, the DRT gene may play a role in neuroblastoma and small cell lung carcinoma (SCLC) tumorigenesis. By fluorescence in situ hybridization, Saito

et al. (1995) demonstrated that the ERK gene is located in chromosomal region 1p36.1. They showed that the homologous genes are located on mouse 4D2.2–D3 and rat 5q36.13, both of which are regions with conserved linkage homology to human chromosome 1p. Animal model experiments lend further support to the function of EPHB2. Halford et al. (2000) generated mice deficient in Ryk (OMIM Ref. No. 600524) and found that they had a distinctive craniofacial appearance, shortened limbs, and postnatal mortality due to feeding and respiratory complications associated with a complete cleft of the secondary palate. Consistent with cleft palate phenocopy in Ephb2/Ephb3 (OMIM Ref. No. 601839)–deficient mice and the role of a Drosophila Ryk ortholog, 'Derailed,' in the transduction of repulsive axon pathfinding cues, biochemical data implicated Ryk in signaling mediated by Eph receptors and cell junction–associated Af6 (OMIM Ref. No. 159559). Halford et al. (2000) concluded that their findings highlighted the importance of signal crosstalk between members of different RTK subfamilies.

[23579] It is appreciated that the abovementioned animal model for EPHB2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appre–



ciated from the publications sited hereinbelow.

[23580] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23581] Ikegaki, N.; Tang, X. X.; Liu, X.-G.; Biegel, J. A.; Allen, C.; Yoshioka, A.; Sulman, E. P.; Brodeur, G. M.; Pleasure, D. E. : Molecular characterization and chromosomal localization of DRT (EPHT3): a developmentally regulated human protein-tyrosine kinase gene of the EPH family. Hum. Molec. Genet. 4: 2033-2045, 1995. ; and

[23582] Halford, M. M.; Armes, J.; Buchert, M.; Meskenaite, V.; Grail, D.; Hibbs, M. L.; Wilks, A. F.; Farlie, P. G.; Newgreen, D. F.; Hovens, C. M.; Stacker, S. A. : Ryk-deficient mice exhibit.

[23583] Further studies establishing the function and utilities of EPHB2 are found in John Hopkins OMIM database record ID 600997, and in sited publications numbered 12700, 12675-7763, 7565, 7764, 7877, 7878-7879, 776 and 7880 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Exonuclease 1 (EXO1, Accession NM\_130398) is another VGAM533 host target gene. EXO1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded

by EXO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EXO1 BINDING SITE, designated SEQ ID:28182, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23584] Another function of VGAM533 is therefore inhibition of Exonuclease 1 (EXO1, Accession NM\_130398), a gene which excise and replace mismatched segments. Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EXO1. The function of EXO1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM399.CNIL (Accession NM\_005776) is another VGAM533 host target gene. CNIL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNIL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNIL BINDING SITE, designated SEQ ID:12354, to the nucleotide se-

quence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23585] Another function of VGAM533 is therefore inhibition of CNIL (Accession NM\_005776). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNIL. Dickkopf Homolog 2 (*Xenopus laevis*) (DKK2, Accession NM\_014421) is another VGAM533 host target gene. DKK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKK2 BINDING SITE, designated SEQ ID:15775, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23586] Another function of VGAM533 is therefore inhibition of Dickkopf Homolog 2 (*Xenopus laevis*) (DKK2, Accession NM\_014421). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKK2. FLJ10307 (Accession NM\_018053) is another VGAM533 host target gene. FLJ10307 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by FLJ10307, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10307 BINDING SITE, designated SEQ ID:19812, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23587] Another function of VGAM533 is therefore inhibition of FLJ10307 (Accession NM\_018053). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10307. General Transcription Factor IIIC, Polypeptide 1, Alpha 220kDa (GTF3C1, Accession NM\_001520) is another VGAM533 host target gene. GTF3C1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GTF3C1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GTF3C1 BINDING SITE, designated SEQ ID:7261, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23588] Another function of VGAM533 is therefore inhibition of General Transcription Factor IIIC, Polypeptide 1, Alpha 220kDa (GTF3C1, Accession NM\_001520). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GTF3C1. HSA277841 (Accession NM\_018553) is another VGAM533 host target gene. HSA277841 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSA277841, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSA277841 BINDING SITE, designated SEQ ID:20634, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23589] Another function of VGAM533 is therefore inhibition of HSA277841 (Accession NM\_018553). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSA277841. KIAA0189 (Accession NM\_014725) is another VGAM533 host target gene. KIAA0189 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0189, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0189 BINDING SITE, designated SEQ ID:16318, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23590] Another function of VGAM533 is therefore inhibition of KIAA0189 (Accession NM\_014725). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0189. KIAA0552 (Accession NM\_014731) is another VGAM533 host target gene. KIAA0552 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0552, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0552 BINDING SITE, designated SEQ ID:16347, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23591] Another function of VGAM533 is therefore inhibition of KIAA0552 (Accession NM\_014731). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0552. KIAA0712 (Accession NM\_014715) is another VGAM533 host target gene. KIAA0712 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0712, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0712 BINDING SITE, designated SEQ ID:16265, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23592] Another function of VGAM533 is therefore inhibition of KIAA0712 (Accession NM\_014715). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0712. WWP1 (Accession XM\_087357) is another VGAM533 host target gene. WWP1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by WWP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WWP1 BINDING SITE, designated SEQ ID:39191, to the nucleotide sequence of

VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23593] Another function of VGAM533 is therefore inhibition of WWP1 (Accession XM\_087357). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WWP1. LOC137492 (Accession XM\_059910) is another VGAM533 host target gene. LOC137492 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC137492, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC137492 BINDING SITE, designated SEQ ID:37106, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23594] Another function of VGAM533 is therefore inhibition of LOC137492 (Accession XM\_059910). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC137492. LOC144776 (Accession XM\_084964) is another VGAM533 host target gene. LOC144776 BINDING SITE is HOST TARGET binding site found in the 3' un-



translated region of mRNA encoded by LOC144776, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144776 BINDING SITE, designated SEQ ID:37787, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23595] Another function of VGAM533 is therefore inhibition of LOC144776 (Accession XM\_084964). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144776. LOC146420 (Accession XM\_096996) is another VGAM533 host target gene. LOC146420 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146420 BINDING SITE, designated SEQ ID:40694, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23596] Another function of VGAM533 is therefore inhibition of LOC146420 (Accession XM\_096996). Accordingly, utilities

of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146420. LOC158402 (Accession XM\_098936) is another VGAM533 host target gene. LOC158402 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158402, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158402 BINDING SITE, designated SEQ ID:41978, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23597] Another function of VGAM533 is therefore inhibition of LOC158402 (Accession XM\_098936). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158402. LOC257438 (Accession XM\_168338) is another VGAM533 host target gene. LOC257438 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257438, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC257438 BINDING SITE, designated SEQ ID:45106, to the nucleotide sequence of VGAM533 RNA, herein designated VGAM RNA, also designated SEQ ID:3244.

[23598] Another function of VGAM533 is therefore inhibition of LOC257438 (Accession XM\_168338). Accordingly, utilities of VGAM533 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257438. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 534 (VGAM534) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23599] VGAM534 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM534 was detected is described hereinabove with reference to Figs. 1–8.

[23600] VGAM534 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Orgyia Pseudotsugata Single Capsid Nuclear Polyhedrosis Virus. VGAM534 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23601] VGAM534 gene encodes a VGAM534 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM534 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM534 precursor RNA is designated SEQ ID:520, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:520 is located at position 23857 relative to the genome of Orgyia Pseudotsugata Single Capsid Nuclear Polyhedrosis Virus.

[23602] VGAM534 precursor RNA folds onto itself, forming VGAM534 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23603] An enzyme complex designated DICER COMPLEX, `dices` the VGAM534 folded precursor RNA into VGAM534 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM534 RNA is designated SEQ ID:3245, and is provided hereinbelow with reference to the sequence listing part.

[23604] VGAM534 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM534 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM534 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23605] VGAM534 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM534 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM534 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM534 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM534 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23606] The complementary binding of VGAM534 RNA, herein designated VGAM RNA, to host target binding sites on VGAM534 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM534 host target RNA into VGAM534 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23607] It is appreciated that VGAM534 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM534 host target genes. The mRNA of each one of this plurality of VGAM534 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM534 RNA, herein designated VGAM RNA, and which when bound by VGAM534 RNA causes inhibition of translation of respective one or more VGAM534 host target proteins.

[23608] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM534 gene, herein designated VGAM GENE, on one or more VGAM534 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23609] It is yet further appreciated that a function of VGAM534 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of viral infection by Orgyia Pseudotsugata Single Capsid Nuclear Polyhedrosis Virus. Specific functions, and accordingly utilities, of VGAM534 correlate with, and may be deduced from, the identity of the host target genes which VGAM534 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23610] Nucleotide sequences of the VGAM534 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM534 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM534 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM534 are further described hereinbelow with reference to Table 1.

[23611] Nucleotide sequences of host target binding sites, such as



BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM534 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM534 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23612] As mentioned hereinabove with reference to Fig. 1, a function of VGAM534 gene, herein designated VGAM is inhibition of expression of VGAM534 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM534 correlate with, and may be deduced from, the identity of the target genes which VGAM534 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23613] Forkhead Box D2 (FOXD2, Accession NM\_004474) is a VGAM534 host target gene. FOXD2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FOXD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOXD2 BINDING SITE, designated SEQ ID:10790, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3245.

[23614] A function of VGAM534 is therefore inhibition of Forkhead Box D2 (FOXD2, Accession NM\_004474). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOXD2. Syndecan 1 (SDC1, Accession NM\_002997) is another VGAM534 host target gene. SDC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDC1 BINDING SITE, designated SEQ ID:8887, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23615] Another function of VGAM534 is therefore inhibition of Syndecan 1 (SDC1, Accession NM\_002997), a gene which mediates cell behaviors like cell adhesion, action of growth factors. Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDC1. The function of SDC1 has been established by previous studies. Sanderson et al. (1989) showed that Sdc1 is expressed in mouse only when

and where B lymphocytes associate with extracellular matrix, namely as B-cell precursors in bone marrow and as immobilized plasma cells in interstitial matrices. Expression is lost immediately before maturation and release of B lymphocytes into the circulation and is absent on circulating and mature peripheral B lymphocytes. SDC1 is re-expressed on differentiated plasma cells and is a marker for cells secreting immunoglobulin. By probing a breast epithelial cell line cDNA library with mouse syndecan probes, Mali et al. (1990) obtained a cDNA encoding human SDC1. Sequence analysis predicted that the 310-amino acid human protein is 77% identical to the mouse sequence. SDC1 has an ectodomain, a 25-residue transmembrane domain, and a 34-residue cytoplasmic domain, which are 70%, 96%, and 100% identical to those of the mouse protein, respectively. The ectodomain is preceded by an N-terminal signal peptide and contains 5 potential glycosaminoglycan-attachment sites, 1 potential N-glycosylation site, and a dibasic lys-arg cleavage site adjacent to the transmembrane domain. Northern blot analysis revealed expression of 2.6- and 3.4-kb SDC1 transcripts in mammary epithelial and carcinoma cells and in fetal skin; a 4.5-kb transcript was detected in brain.

Animal model experiments lend further support to the function of SDC1. Reizes et al. (2001) found that transgenic expression in the hypothalamus of Sdc1 produced mice with hyperphagia and maturity-onset obesity resembling mice with reduced action of alpha-melanocyte-stimulating hormone (alpha-MSH; OMIM Ref. No. 155555). Via their heparan sulfate chains, syndecans potentiate the action of agouti-related protein (OMIM Ref. No. 602311) and agouti signaling protein (OMIM Ref. No. 600201), endogenous inhibitors of alpha-MSH. In wild-type mice, Sdc3 (OMIM Ref. No. 186357), the predominantly neural syndecan, was expressed in hypothalamic regions that control energy balance. Food deprivation increased hypothalamic Sdc3 levels several-fold. Sdc3 null mice, which otherwise appeared normal, responded to food deprivation with markedly reduced reflex hyperphagia. Reizes et al. (2001) proposed that oscillation of hypothalamic SDC3 levels physiologically modulates feeding behavior.

[23616] It is appreciated that the abovementioned animal model for SDC1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[23617] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23618] Alexander, C. M.; Reichsman, F.; Hinkes, M. T.; Lincecum, J.; Becker, K. A.; Cumberledge, S.; Bernfield, M. : Syndecan-1 is required for Wnt-1-induced mammary tumorigenesis in mice. *Nature Genet.* 25: 329-332, 2000. ; and

[23619] Mali, M.; Jaakkola, P.; Arvilommi, A.-M.; Jalkanen, M. : Sequence of human syndecan indicates a novel gene family of integral membrane proteoglycans. *J. Biol. Chem.* 265: 6884-6889, 199.

[23620] Further studies establishing the function and utilities of SDC1 are found in John Hopkins OMIM database record ID 186355, and in cited publications numbered 10500-1050 and 11616 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CSR1 (Accession NM\_016240) is another VGAM534 host target gene. CSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSR1 BINDING SITE, designated SEQ ID:18360,

to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23621] Another function of VGAM534 is therefore inhibition of CSR1 (Accession NM\_016240). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSR1. DKFZP434P211 (Accession NM\_014549) is another VGAM534 host target gene. DKFZP434P211 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434P211, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434P211 BINDING SITE, designated SEQ ID:15869, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23622] Another function of VGAM534 is therefore inhibition of DKFZP434P211 (Accession NM\_014549). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434P211. DKFZP586B2420 (Accession XM\_059482) is another VGAM534 host target gene. DKFZP586B2420 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by DKFZP586B2420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586B2420 BINDING SITE, designated SEQ ID:37009, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23623] Another function of VGAM534 is therefore inhibition of DKFZP586B2420 (Accession XM\_059482). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586B2420. FBX30 (Accession NM\_033182) is another VGAM534 host target gene. FBX30 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FBX30, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBX30 BINDING SITE, designated SEQ ID:27042, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23624] Another function of VGAM534 is therefore inhibition of

FBX30 (Accession NM\_033182). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBX30. HSPC043 (Accession XM\_041943) is another VGAM534 host target gene. HSPC043 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HSPC043, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC043 BINDING SITE, designated SEQ ID:33636, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23625] Another function of VGAM534 is therefore inhibition of HSPC043 (Accession XM\_041943). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC043. KIAA0495 (Accession XM\_031397) is another VGAM534 host target gene. KIAA0495 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0495, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of KIAA0495 BINDING SITE, designated SEQ ID:31356, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23626] Another function of VGAM534 is therefore inhibition of KIAA0495 (Accession XM\_031397). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0495. KIAA1243 (Accession XM\_057057) is another VGAM534 host target gene. KIAA1243 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1243, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1243 BINDING SITE, designated SEQ ID:36471, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23627] Another function of VGAM534 is therefore inhibition of KIAA1243 (Accession XM\_057057). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1243. LOC157918 (Accession XM\_098842) is another

VGAM534 host target gene. LOC157918 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157918, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157918 BINDING SITE, designated SEQ ID:41898, to the nucleotide sequence of VGAM534 RNA, herein designated VGAM RNA, also designated SEQ ID:3245.

[23628] Another function of VGAM534 is therefore inhibition of LOC157918 (Accession XM\_098842). Accordingly, utilities of VGAM534 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157918. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 535 (VGAM535) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23629] VGAM535 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM535 was detected is described

hereinabove with reference to Figs. 1–8.

[23630] VGAM535 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hendra Virus. VGAM535 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23631] VGAM535 gene encodes a VGAM535 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM535 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM535 precursor RNA is designated SEQ ID:521, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:521 is located at position 9666 relative to the genome of Hendra Virus.

[23632] VGAM535 precursor RNA folds onto itself, forming VGAM535 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed–reversed sequence of the nu–

cleotide sequence of the second half thereof.

[23633] An enzyme complex designated DICER COMPLEX, `dices` the VGAM535 folded precursor RNA into VGAM535 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM535 RNA is designated SEQ ID:3246, and is provided hereinbelow with reference to the sequence listing part.

[23634] VGAM535 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM535 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM535 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23635] VGAM535 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM535 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM535 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM535 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM535 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23636] The complementary binding of VGAM535 RNA, herein designated VGAM RNA, to host target binding sites on VGAM535 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM535 host target RNA into VGAM535 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23637] It is appreciated that VGAM535 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM535 host target genes. The mRNA of each one of this plurality of VGAM535 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM535 RNA, herein designated VGAM RNA, and which when bound by VGAM535 RNA causes inhibition of translation of respective one or more VGAM535 host target proteins.

[23638] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM535 gene, herein designated VGAM GENE, on one or more VGAM535 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23639] It is yet further appreciated that a function of VGAM535 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of viral infection by Hendra Virus. Specific functions, and accordingly utilities, of VGAM535 correlate with, and may be deduced from, the identity of the host target genes which VGAM535 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23640] Nucleotide sequences of the VGAM535 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM535 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM535 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM535 are further described hereinbelow with reference to Table 1.

[23641] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM535 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM535 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23642] As mentioned hereinabove with reference to Fig. 1, a function of VGAM535 gene, herein designated VGAM is inhibition of expression of VGAM535 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM535 correlate with, and may be deduced from, the identity of the target genes which VGAM535 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23643] Pleckstrin Homology-like Domain, Family A, Member 3 (PHLDA3, Accession NM\_012396) is a VGAM535 host target gene. PHLDA3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PHLDA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.



Table 2 illustrates the complementarity of the nucleotide sequences of PHLDA3 BINDING SITE, designated SEQ ID:14760, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23644] A function of VGAM535 is therefore inhibition of Pleckstrin Homology-like Domain, Family A, Member 3 (PHLDA3, Accession NM\_012396). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PHLDA3. Pim-2 Oncogene (PIM2, Accession XM\_010208) is another VGAM535 host target gene. PIM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIM2 BINDING SITE, designated SEQ ID:30135, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23645] Another function of VGAM535 is therefore inhibition of Pim-2 Oncogene (PIM2, Accession XM\_010208). Accordingly, utilities of VGAM535 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with PIM2. DKFZP566G1424 (Accession XM\_097771) is another VGAM535 host target gene. DKFZP566G1424 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZP566G1424, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566G1424 BINDING SITE, designated SEQ ID:41116, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23646] Another function of VGAM535 is therefore inhibition of DKFZP566G1424 (Accession XM\_097771). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566G1424. FLJ11370 (Accession NM\_024961) is another VGAM535 host target gene. FLJ11370 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11370, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

FLJ11370 BINDING SITE, designated SEQ ID:24517, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23647] Another function of VGAM535 is therefore inhibition of FLJ11370 (Accession NM\_024961). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11370. MIG (Accession NM\_002416) is another VGAM535 host target gene. MIG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MIG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MIG BINDING SITE, designated SEQ ID:8247, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23648] Another function of VGAM535 is therefore inhibition of MIG (Accession NM\_002416). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MIG. Phosphatase, Orphan 1 (phospho1, Accession XM\_091572) is another VGAM535 host target gene. phospho1 BINDING SITE is HOST TARGET binding site found in

the 5` untranslated region of mRNA encoded by phospho1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of phospho1 BINDING SITE, designated SEQ ID:40059, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23649] Another function of VGAM535 is therefore inhibition of Phosphatase, Orphan 1 (phospho1, Accession XM\_091572). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with phospho1. Zinc Finger Protein 262 (ZNF262, Accession NM\_005095) is another VGAM535 host target gene. ZNF262 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZNF262, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF262 BINDING SITE, designated SEQ ID:11559, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23650] Another function of VGAM535 is therefore inhibition of Zinc Finger Protein 262 (ZNF262, Accession NM\_005095). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF262. LOC144308 (Accession XM\_096575) is another VGAM535 host target gene. LOC144308 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144308, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144308 BINDING SITE, designated SEQ ID:40405, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23651] Another function of VGAM535 is therefore inhibition of LOC144308 (Accession XM\_096575). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144308. LOC149414 (Accession XM\_097635) is another VGAM535 host target gene. LOC149414 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149414, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149414 BINDING SITE, designated SEQ ID:40988, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23652] Another function of VGAM535 is therefore inhibition of LOC149414 (Accession XM\_097635). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149414. LOC196527 (Accession XM\_113743) is another VGAM535 host target gene. LOC196527 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196527, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196527 BINDING SITE, designated SEQ ID:42401, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23653] Another function of VGAM535 is therefore inhibition of LOC196527 (Accession XM\_113743). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC196527. LOC199858 (Accession XM\_114040) is another VGAM535 host target gene. LOC199858 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC199858, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199858 BINDING SITE, designated SEQ ID:42629, to the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23654] Another function of VGAM535 is therefore inhibition of LOC199858 (Accession XM\_114040). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199858. LOC222134 (Accession XM\_168432) is another VGAM535 host target gene. LOC222134 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC222134, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222134 BINDING SITE, designated SEQ ID:45169, to

the nucleotide sequence of VGAM535 RNA, herein designated VGAM RNA, also designated SEQ ID:3246.

[23655] Another function of VGAM535 is therefore inhibition of LOC222134 (Accession XM\_168432). Accordingly, utilities of VGAM535 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222134. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 536 (VGAM536) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23656] VGAM536 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM536 was detected is described hereinabove with reference to Figs. 1–8.

[23657] VGAM536 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ateline Herpesvirus 3. VGAM536 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23658] VGAM536 gene encodes a VGAM536 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM536 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM536 precursor RNA is designated SEQ ID:522, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:522 is located at position 103974 relative to the genome of Ate-line Herpesvirus 3.

[23659] VGAM536 precursor RNA folds onto itself, forming VGAM536 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23660] An enzyme complex designated DICER COMPLEX, `dices` the VGAM536 folded precursor RNA into VGAM536 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM536 RNA is designated SEQ ID:3247, and is provided hereinbelow with reference to the sequence listing part.

[23661] VGAM536 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM536 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM536 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[23662] VGAM536 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM536 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM536 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM536 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM536 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23663] The complementary binding of VGAM536 RNA, herein designated VGAM RNA, to host target binding sites on VGAM536 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM536 host target RNA into VGAM536 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23664] It is appreciated that VGAM536 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM536 host target genes. The mRNA of each one of this plurality of VGAM536 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM536 RNA, herein designated VGAM RNA, and which when bound by VGAM536 RNA causes inhibition of translation of respective one or more VGAM536 host target proteins.

[23665] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM536 gene, herein designated VGAM GENE, on one or more VGAM536 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[23666] It is yet further appreciated that a function of VGAM536 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM536 include diagnosis, prevention and treatment of viral infection by Ateline Herpesvirus 3. Specific functions, and accordingly utilities, of VGAM536 correlate with, and may be deduced from, the identity of the host target genes which VGAM536 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23667] Nucleotide sequences of the VGAM536 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM536 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM536 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM536 are further described hereinbelow with reference to Table 1.

[23668] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM536 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM536 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23669] As mentioned hereinabove with reference to Fig. 1, a function of VGAM536 gene, herein designated VGAM is inhibition of expression of VGAM536 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM536 correlate with, and may be deduced from, the identity of the target genes which VGAM536 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23670] V-akt Murine Thymoma Viral Oncogene Homolog 1 (AKT1, Accession NM\_005163) is a VGAM536 host target gene. AKT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKT1 BINDING SITE, designated SEQ ID:11649, to the nucleotide sequence of VGAM536 RNA, herein designated VGAM RNA, also designated SEQ ID:3247.

[23671] A function of VGAM536 is therefore inhibition of V-akt Murine Thymoma Viral Oncogene Homolog 1 (AKT1, Ac-

cession NM\_005163), a gene which Serine–threonine protein kinase. Accordingly, utilities of VGAM536 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKT1. The function of AKT1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM188.KIAA0534 (Accession XM\_049349) is another VGAM536 host target gene. KIAA0534 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0534, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0534 BINDING SITE, designated SEQ ID:35376, to the nucleotide sequence of VGAM536 RNA, herein designated VGAM RNA, also designated SEQ ID:3247.

[23672] Another function of VGAM536 is therefore inhibition of KIAA0534 (Accession XM\_049349). Accordingly, utilities of VGAM536 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0534. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 537 (VGAM537) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23673] VGAM537 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM537 was detected is described hereinabove with reference to Figs. 1–8.

[23674] VGAM537 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ateline Herpesvirus 3. VGAM537 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23675] VGAM537 gene encodes a VGAM537 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM537 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM537 precursor RNA is designated SEQ ID:523, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:523 is located at position 103754 relative to the genome of Ate–



line Herpesvirus 3.

[23676] VGAM537 precursor RNA folds onto itself, forming VGAM537 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23677] An enzyme complex designated DICER COMPLEX, `dices` the VGAM537 folded precursor RNA into VGAM537 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM537 RNA is designated SEQ ID:3248, and is provided hereinbelow with reference to the sequence listing part.

[23678] VGAM537 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM537 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM537 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23679] VGAM537 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM537 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM537 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM537 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM537 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23680] The complementary binding of VGAM537 RNA, herein designated VGAM RNA, to host target binding sites on VGAM537 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM537 host target RNA into VGAM537 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23681] It is appreciated that VGAM537 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM537 host target genes. The mRNA of each one of this plurality of VGAM537 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM537 RNA, herein designated VGAM RNA, and which when bound by VGAM537 RNA causes inhibition of translation of respective one or more VGAM537 host target proteins.

[23682] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM537 gene, herein designated VGAM GENE, on one or more VGAM537 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23683] It is yet further appreciated that a function of VGAM537 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM537 include diagnosis, prevention and treatment of viral infection by Ateline Herpesvirus 3. Specific functions, and accordingly utilities, of VGAM537 cor-

relate with, and may be deduced from, the identity of the host target genes which VGAM537 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23684] Nucleotide sequences of the VGAM537 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM537 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM537 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM537 are further described hereinbelow with reference to Table 1.

[23685] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM537 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM537 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23686] As mentioned hereinabove with reference to Fig. 1, a function of VGAM537 gene, herein designated VGAM is inhibition of expression of VGAM537 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM537 correlate with, and may be deduced

from, the identity of the target genes which VGAM537 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23687] G Protein-coupled Receptor 18 (GPR18, Accession NM\_005292) is a VGAM537 host target gene. GPR18 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by GPR18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR18 BINDING SITE, designated SEQ ID:11783, to the nucleotide sequence of VGAM537 RNA, herein designated VGAM RNA, also designated SEQ ID:3248.

[23688] A function of VGAM537 is therefore inhibition of G Protein-coupled Receptor 18 (GPR18, Accession NM\_005292). Accordingly, utilities of VGAM537 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR18. LOC148894 (Accession XM\_097542) is another VGAM537 host target gene. LOC148894 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC148894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148894 BINDING SITE, designated SEQ ID:40914, to the nucleotide sequence of VGAM537 RNA, herein designated VGAM RNA, also designated SEQ ID:3248.

[23689] Another function of VGAM537 is therefore inhibition of LOC148894 (Accession XM\_097542). Accordingly, utilities of VGAM537 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148894. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 538 (VGAM538) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23690] VGAM538 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM538 was detected is described hereinabove with reference to Figs. 1–8.

[23691] VGAM538 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ateline Herpesvirus 3. VGAM538 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[23692] VGAM538 gene encodes a VGAM538 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM538 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM538 precursor RNA is designated SEQ ID:524, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:524 is located at position 65909 relative to the genome of Ate-line Herpesvirus 3.

[23693] VGAM538 precursor RNA folds onto itself, forming VGAM538 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23694] An enzyme complex designated DICER COMPLEX, `dices` the VGAM538 folded precursor RNA into VGAM538 RNA,



herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM538 RNA is designated SEQ ID:3249, and is provided hereinbelow with reference to the sequence listing part.

[23695] VGAM538 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM538 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM538 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23696] VGAM538 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM538 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM538 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM538 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM538 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23697] The complementary binding of VGAM538 RNA, herein designated VGAM RNA, to host target binding sites on VGAM538 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM538 host target RNA into VGAM538 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[23698] It is appreciated that VGAM538 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM538 host target genes. The mRNA of each one of this plurality of VGAM538 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM538 RNA, herein designated VGAM RNA, and which when bound by VGAM538 RNA causes inhibition of translation of respective one or more VGAM538 host target proteins.

[23699] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM538 gene, herein designated VGAM GENE, on one or more VGAM538 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23700] It is yet further appreciated that a function of VGAM538 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of viral infection by Ateline Herpesvirus 3. Specific functions, and accordingly utilities, of VGAM538 correlate with, and may be deduced from, the identity of the host target genes which VGAM538 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23701] Nucleotide sequences of the VGAM538 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM538 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM538 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM538 are further described hereinbelow with reference to Table 1.

[23702] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM538 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM538 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23703] As mentioned hereinabove with reference to Fig. 1, a function of VGAM538 gene, herein designated VGAM is inhibition of expression of VGAM538 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM538 correlate with, and may be deduced from, the identity of the target genes which VGAM538 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23704] Annexin A8 (ANXA8, Accession NM\_001630) is a VGAM538 host target gene. ANXA8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ANXA8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANXA8 BINDING SITE, designated SEQ ID:7341, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3249.

[23705] A function of VGAM538 is therefore inhibition of Annexin A8 (ANXA8, Accession NM\_001630), a gene which acts as an indirect inhibitor of the thromboplastin-specific complex, which is involved in the blood coagulation cascade. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANXA8. The function of ANXA8 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM372. CERD4 (Accession NM\_012074) is another VGAM538 host target gene. CERD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CERD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CERD4 BINDING SITE, designated SEQ ID:14347, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23706] Another function of VGAM538 is therefore inhibition of CERD4 (Accession NM\_012074). Accordingly, utilities of

VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CERD4. Collagen, Type IV, Alpha 3 (Goodpasture antigen) (COL4A3, Accession NM\_031363) is another VGAM538 host target gene. COL4A3 BINDING SITE1 through COL4A3 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by COL4A3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COL4A3 BINDING SITE1 through COL4A3 BINDING SITE3, designated SEQ ID:25355, SEQ ID:25361 and SEQ ID:5548 respectively, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23707] Another function of VGAM538 is therefore inhibition of Collagen, Type IV, Alpha 3 (Goodpasture antigen) (COL4A3, Accession NM\_031363). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COL4A3. Dual Specificity Phosphatase 5 (DUSP5, Accession NM\_004419) is another VGAM538 host target gene. DUSP5 BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by DUSP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DUSP5 BINDING SITE, designated SEQ ID:10685, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23708] Another function of VGAM538 is therefore inhibition of Dual Specificity Phosphatase 5 (DUSP5, Accession NM\_004419), a gene which displays phosphatase activity toward several substrates. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DUSP5. The function of DUSP5 has been established by previous studies. The VH1 phosphatase encoded by vaccinia virus is a dual-specificity protein-tyrosine phosphatase (OMIM Ref. No. PTPase) which hydrolyzes substrates phosphorylated on both tyrosine and serine/threonine residues. VH1-like PTPases have been identified in humans and other organisms. See DUSP1 (OMIM Ref. No. 600714). To identify additional human dual-specificity PTPases, Martell et al. (1994) screened a genomic library with a partial



DUSP1 cDNA. They isolated several novel PTPase genes, including 1 which they designated HVH3 for human VH1-like PTPase-3. Kwak and Dixon (1995) cloned human placental HVH3 cDNAs and reported that the predicted protein has 384 amino acids. Using immunofluorescence, they determined that epitope-tagged HVH3 is localized primarily in the nucleus of mammalian cells. Ishibashi et al. (1994) isolated HVH3 cDNAs from a human mammary epithelial cell cDNA library and found that the predicted protein has 397 amino acids. In vitro, recombinant protein containing the catalytic domain of HVH3 displayed phosphatase activity toward several substrates. The highest relative activity was toward ERK1 (OMIM Ref. No. 601795), suggesting that it may be a target for HVH3 activity in vivo. Northern blot analysis revealed that HVH3 is expressed as a 2.5-kb mRNA in a variety of tissues, with the highest levels in pancreas and brain. HVH3 expression was induced by serum stimulation of fibroblasts and by heat shock, with similar kinetics to those observed with DUSP1. As has been proposed for other dual-specificity PTPases like DUSP1 and DUSP2 (OMIM Ref. No. 603068), Ishibashi et al. (1994) suggested that the induction of HVH3 may lead to the deactivation of mitogen- or stress-

activated protein kinases, thereby restoring these signaling pathways to their mitogen- or stress-sensitive state. By fluorescence in situ hybridization, Martell et al. (1994) mapped the HVH3 gene to 10q25

[23709] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23710] Ishibashi, T.; Bottaro, D. P.; Michieli, P.; Kelley, C. A.; Aaronson, S. A. : A novel dual specificity phosphatase induced by serum stimulation and heat shock. J. Biol. Chem. 269: 29897–29902, 1994. ; and

[23711] Martell, K. J.; Kwak, S.; Hakes, D. J.; Dixon, J. E.; Trent, J. M. : Chromosomal localization of four human VH1-like protein-tyrosine phosphatases. Genomics 22: 462–464, 1994.

[23712] Further studies establishing the function and utilities of DUSP5 are found in John Hopkins OMIM database record ID 603069, and in cited publications numbered 8850–885 and 10055 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Eukaryotic Translation Initiation Factor 1A, Y Chromosome (EIF1AY, Accession NM\_004681) is another VGAM538 host target gene. EIF1AY BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF1AY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF1AY BINDING SITE, designated SEQ ID:11045, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23713] Another function of VGAM538 is therefore inhibition of Eukaryotic Translation Initiation Factor 1A, Y Chromosome (EIF1AY, Accession NM\_004681). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF1AY. Echinoderm Microtubule Associated Protein Like 1 (EML1, Accession XM\_007243) is another VGAM538 host target gene. EML1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EML1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EML1 BINDING SITE, designated SEQ ID:30037, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23714] Another function of VGAM538 is therefore inhibition of Echinoderm Microtubule Associated Protein Like 1 (EML1, Accession XM\_007243). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EML1. Fibroblast Growth Factor Receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome) (FGFR1, Accession NM\_000604) is another VGAM538 host target gene. FGFR1 BINDING SITE1 through FGFR1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGFR1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGFR1 BINDING SITE1 through FGFR1 BINDING SITE3, designated SEQ ID:6209, SEQ ID:23374 and SEQ ID:17980 respectively, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23715] Another function of VGAM538 is therefore inhibition of Fibroblast Growth Factor Receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome) (FGFR1, Accession NM\_000604). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with FGFR1. Histone Deacetylase 4 (HDAC4, Accession NM\_006037) is another VGAM538 host target gene. HDAC4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HDAC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HDAC4 BINDING SITE, designated SEQ ID:12667, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23716] Another function of VGAM538 is therefore inhibition of Histone Deacetylase 4 (HDAC4, Accession NM\_006037), a gene which is responsible for the deacetylation of lysine residues on the n-terminal part of the core histones and may mediate transcriptional regulation. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HDAC4. The function of HDAC4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM264. Itchy Homolog E3 Ubiquitin Protein Ligase (mouse) (ITCH, Accession NM\_031483) is another

VGAM538 host target gene. ITCH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITCH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITCH BINDING SITE, designated SEQ ID:25563, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23717] Another function of VGAM538 is therefore inhibition of Itchy Homolog E3 Ubiquitin Protein Ligase (mouse) (ITCH, Accession NM\_031483), a gene which accepts ubiquitin from an e2 ubiquitin-conjugating enzyme in the form of a thioester and then directly transfers the ubiquitin to targeted substrates. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITCH. The function of ITCH and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM206. Lipase A, Lysosomal Acid, Cholesterol Esterase (Wolman disease) (LIPA, Accession NM\_000235) is another VGAM538 host target gene. LIPA BINDING SITE is HOST TARGET binding

site found in the 3' untranslated region of mRNA encoded by LIPA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LIPA BINDING SITE, designated SEQ ID:5746, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23718] Another function of VGAM538 is therefore inhibition of Lipase A, Lysosomal Acid, Cholesterol Esterase (Wolman disease) (LIPA, Accession NM\_000235). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LIPA. Neuroblastoma RAS Viral (v-ras) Oncogene Homolog (NRAS, Accession NM\_002524) is another VGAM538 host target gene. NRAS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRAS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRAS BINDING SITE, designated SEQ ID:8362, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23719] Another function of VGAM538 is therefore inhibition of Neuroblastoma RAS Viral (v-ras) Oncogene Homolog (NRAS, Accession NM\_002524), a gene which ras proteins bind gdp/gtp and possess intrinsic gtpase activity. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRAS. The function of NRAS and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM351. Oxidative-stress Responsive 1 (OSR1, Accession NM\_005109) is another VGAM538 host target gene. OSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSR1 BINDING SITE, designated SEQ ID:11591, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23720] Another function of VGAM538 is therefore inhibition of Oxidative-stress Responsive 1 (OSR1, Accession NM\_005109), a gene which mediates stress-activated sig-



nals. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OSR1. The function of OSR1 has been established by previous studies. The 3p22–p21.3 chromosomal region is one of 3 regions of 3p that is commonly deleted in various carcinomas. By analyzing a cloned segment from this region, Tamari et al. (1999) identified a novel gene that they designated OSR1 (oxidative stress–responsive–1) because the predicted 527–amino acid protein shares 39% identity with Ste20/oxidant stress–response kinase–1 (OMIM Ref. No. 602255). The OSR1 gene contains 18 exons and spans approximately 90 kb. Northern blot analysis revealed that OSR1 was expressed as a 4.6–kb major transcript in all tissues tested. A less abundant 7.5–kb mRNA was detected in heart and skeletal muscle. Daigo et al. (1999) reported that the OSR1 gene is located between the OCTL1 (OMIM Ref. No. 604047) and MYD88 (OMIM Ref. No. 602170) genes on 3p22–p21.3.

[23721] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23722] Tamari, M.; Daigo, Y.; Nakamura, Y. : Isolation and char–

acterization of a novel serine threonine kinase gene on chromosome 3q22–21.3. J. Hum. Genet. 44: 116–120, 1999. ; and

[23723] Daigo, Y.; Isomura, M.; Nishiwaki, T.; Tamari, M.; Ishikawa, S.; Kai, M.; Murata, Y.; Takeuchi, K.; Yamane, Y.; Hayashi, R.; Minami, M.; Fujino, M. A.; Hojo, Y.; Uchiyama, I.; Takagi, T.;

[23724] Further studies establishing the function and utilities of OSR1 are found in John Hopkins OMIM database record ID 604046, and in cited publications numbered 9037 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Plexin A2 (PLXNA2, Accession NM\_025179) is another VGAM538 host target gene. PLXNA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLXNA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLXNA2 BINDING SITE, designated SEQ ID:24814, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23725] Another function of VGAM538 is therefore inhibition of

Plexin A2 (PLXNA2, Accession NM\_025179), a gene which is a transmembrane protein. Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLXNA2. The function of PLXNA2 has been established by previous studies. In the course of searching for previously unknown genes on the human X chromosome, Maestrini et al. (1996) identified a cDNA in Xq28 encoding a transmembrane protein that they termed SEX (OMIM Ref. No. 300022). They showed that SEX shares significant homology with the extracellular domain of the receptors encoded by MET and other members of the hepatocyte growth factor (HGF) receptor family. Three other sequences closely related to SEX were identified, 1 of which (designated OCT) was shown by analysis of a panel of human/hamster somatic cell hybrids to map to chromosome 1. The proteins encoded by all 4 genes contained large cytoplasmic domains characterized by a distinctive highly conserved sequence they called the SEX domain. See also 601053 and 601055. Nomenclature: Tamagnone et al. (1999) proposed a novel nomenclature for the genes of the plexin family, which they grouped into the A, B, C, and D subfamilies; the PLXN2 gene was renamed plexin A2 by

them.

[23726] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23727] Maestrini, E.; Tamagnone, L.; Longati, P.; Cremona, O.; Gulisano, M.; Bione, S.; Tamanini, F.; Neel, B. G.; Toniolo, D.; Comoglio, P. M. : A family of transmembrane proteins with homology to the MET–hepatocyte growth factor receptor. *Proc. Nat. Acad. Sci.* 93: 674–678, 1996. ; and

[23728] Tamagnone, L.; Artigiani, S.; Chen, H.; He, Z.; Ming, G.; Song, H.; Chedotal, A.; Winberg, M. L.; Goodman, C. S.; Poo, M.; Tessier–Lavigne, M.; Comoglio, P. M. : Plexins are a large family.

[23729] Further studies establishing the function and utilities of PLXNA2 are found in John Hopkins OMIM database record ID 601054, and in cited publications numbered 7271–7272 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Family 22 (organic cation transporter), Member 5 (SLC22A5, Accession NM\_003060) is another VGAM538 host target gene. SLC22A5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC22A5, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC22A5 BINDING SITE, designated SEQ ID:9027, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23730] Another function of VGAM538 is therefore inhibition of Solute Carrier Family 22 (organic cation transporter), Member 5 (SLC22A5, Accession NM\_003060). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC22A5. Transforming Growth Factor, Beta Receptor II (70/80kDa) (TGFB2, Accession NM\_003242) is another VGAM538 host target gene. TGFB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TGFB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TGFB2 BINDING SITE, designated SEQ ID:9240, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23731] Another function of VGAM538 is therefore inhibition of

Transforming Growth Factor, Beta Receptor II (70/80kDa) (TGFB2, Accession NM\_003242). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TGFB2. Titin (TTN, Accession NM\_133378) is another VGAM538 host target gene. TTN BINDING SITE1 through TTN BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TTN, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TTN BINDING SITE1 through TTN BINDING SITE4, designated SEQ ID:28503, SEQ ID:28505, SEQ ID:28508 and SEQ ID:28518 respectively, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23732] Another function of VGAM538 is therefore inhibition of Titin (TTN, Accession NM\_133378). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TTN. Cysteine and Histidine-rich Domain (CHORD)-containing, Zinc Binding Protein 1 (CHORDC1, Accession NM\_012124) is another VGAM538 host target gene. CHORDC1 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CHORDC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHORDC1 BINDING SITE, designated SEQ ID:14437, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23733] Another function of VGAM538 is therefore inhibition of Cysteine and Histidine-rich Domain (CHORD)-containing, Zinc Binding Protein 1 (CHORDC1, Accession NM\_012124). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHORDC1. DKFZP434C0826 (Accession XM\_097248) is another VGAM538 host target gene. DKFZP434C0826 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZP434C0826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434C0826 BINDING SITE, designated SEQ ID:40845, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3249.

[23734] Another function of VGAM538 is therefore inhibition of DKFZP434C0826 (Accession XM\_097248). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434C0826. DKFZp566H0824 (Accession NM\_017535) is another VGAM538 host target gene. DKFZp566H0824 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp566H0824, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp566H0824 BINDING SITE, designated SEQ ID:18977, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23735] Another function of VGAM538 is therefore inhibition of DKFZp566H0824 (Accession NM\_017535). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp566H0824. DnaJ (Hsp40) Homolog, Subfamily B, Member 4 (DNAJB4, Accession NM\_007034) is another VGAM538 host target gene. DNAJB4 BINDING SITE is HOST



TARGET binding site found in the 5` untranslated region of mRNA encoded by DNAJB4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNAJB4 BINDING SITE, designated SEQ ID:13904, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23736] Another function of VGAM538 is therefore inhibition of DnaJ (Hsp40) Homolog, Subfamily B, Member 4 (DNAJB4, Accession NM\_007034). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNAJB4. FLJ00026 (Accession XM\_036307) is another VGAM538 host target gene. FLJ00026 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ00026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ00026 BINDING SITE, designated SEQ ID:32428, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23737] Another function of VGAM538 is therefore inhibition of FLJ00026 (Accession XM\_036307). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00026. FLJ10081 (Accession NM\_017991) is another VGAM538 host target gene. FLJ10081 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10081, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10081 BINDING SITE, designated SEQ ID:19724, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23738] Another function of VGAM538 is therefore inhibition of FLJ10081 (Accession NM\_017991). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10081. FLJ10702 (Accession NM\_018184) is another VGAM538 host target gene. FLJ10702 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10702, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10702 BINDING SITE, designated SEQ ID:20027, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23739] Another function of VGAM538 is therefore inhibition of FLJ10702 (Accession NM\_018184). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10702. FLJ11850 (Accession NM\_022741) is another VGAM538 host target gene. FLJ11850 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11850, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11850 BINDING SITE, designated SEQ ID:22950, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23740] Another function of VGAM538 is therefore inhibition of FLJ11850 (Accession NM\_022741). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11850.

FLJ13187 (Accession NM\_024613) is another VGAM538 host target gene. FLJ13187 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13187, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13187 BINDING SITE, designated SEQ ID:23870, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23741] Another function of VGAM538 is therefore inhibition of FLJ13187 (Accession NM\_024613). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13187. FLJ20232 (Accession NM\_019008) is another VGAM538 host target gene. FLJ20232 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20232, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20232 BINDING SITE, designated SEQ ID:21083, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3249.

[23742] Another function of VGAM538 is therefore inhibition of FLJ20232 (Accession NM\_019008). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20232. KIAA0229 (Accession XM\_166478) is another VGAM538 host target gene. KIAA0229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0229 BINDING SITE, designated SEQ ID:44399, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23743] Another function of VGAM538 is therefore inhibition of KIAA0229 (Accession XM\_166478). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0229. KIAA0258 (Accession NM\_014785) is another VGAM538 host target gene. KIAA0258 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0258, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0258 BINDING SITE, designated SEQ ID:16652, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23744] Another function of VGAM538 is therefore inhibition of KIAA0258 (Accession NM\_014785). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0258. KIAA0276 (Accession XM\_048199) is another VGAM538 host target gene. KIAA0276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0276 BINDING SITE, designated SEQ ID:35137, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23745] Another function of VGAM538 is therefore inhibition of KIAA0276 (Accession XM\_048199). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0276. KIAA0322 (Accession XM\_166591) is another VGAM538 host target gene. KIAA0322 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0322 BINDING SITE, designated SEQ ID:44560, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23746] Another function of VGAM538 is therefore inhibition of KIAA0322 (Accession XM\_166591). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0322. KIAA0515 (Accession XM\_033380) is another VGAM538 host target gene. KIAA0515 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0515, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0515 BINDING SITE, designated SEQ ID:31924, to the

nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23747] Another function of VGAM538 is therefore inhibition of KIAA0515 (Accession XM\_033380). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0515. KIAA0660 (Accession NM\_012297) is another VGAM538 host target gene. KIAA0660 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0660, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0660 BINDING SITE, designated SEQ ID:14657, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23748] Another function of VGAM538 is therefore inhibition of KIAA0660 (Accession NM\_012297). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0660. KIAA0876 (Accession XM\_035625) is another VGAM538 host target gene. KIAA0876 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by KIAA0876, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0876 BINDING SITE, designated SEQ ID:32298, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23749] Another function of VGAM538 is therefore inhibition of KIAA0876 (Accession XM\_035625). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0876. KIAA0993 (Accession XM\_034413) is another VGAM538 host target gene. KIAA0993 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0993, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0993 BINDING SITE, designated SEQ ID:32081, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23750] Another function of VGAM538 is therefore inhibition of KIAA0993 (Accession XM\_034413). Accordingly, utilities

of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0993. KIAA1023 (Accession NM\_017604) is another VGAM538 host target gene. KIAA1023 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1023, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1023 BINDING SITE, designated SEQ ID:19092, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23751] Another function of VGAM538 is therefore inhibition of KIAA1023 (Accession NM\_017604). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1023. KIAA1265 (Accession XM\_047707) is another VGAM538 host target gene. KIAA1265 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1265, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1265 BINDING SITE, designated SEQ ID:35036, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23752] Another function of VGAM538 is therefore inhibition of KIAA1265 (Accession XM\_047707). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1265. KIAA1493 (Accession XM\_034415) is another VGAM538 host target gene. KIAA1493 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1493, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1493 BINDING SITE, designated SEQ ID:32091, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23753] Another function of VGAM538 is therefore inhibition of KIAA1493 (Accession XM\_034415). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1493. KIAA1804 (Accession XM\_045864) is another VGAM538 host target gene. KIAA1804 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1804, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1804 BINDING SITE, designated SEQ ID:34587, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23754] Another function of VGAM538 is therefore inhibition of KIAA1804 (Accession XM\_045864). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1804. MGC2452 (Accession NM\_032644) is another VGAM538 host target gene. MGC2452 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC2452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2452 BINDING SITE, designated SEQ ID:26372, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23755] Another function of VGAM538 is therefore inhibition of

MGC2452 (Accession NM\_032644). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2452. MGC2477 (Accession NM\_024099) is another VGAM538 host target gene. MGC2477 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC2477, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2477 BINDING SITE, designated SEQ ID:23542, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23756] Another function of VGAM538 is therefore inhibition of MGC2477 (Accession NM\_024099). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2477. Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230) is another VGAM538 host target gene. NUDT11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUDT11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUDT11 BINDING SITE, designated SEQ ID:30141, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23757] Another function of VGAM538 is therefore inhibition of Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUDT11. SEC14-like 1 (*S. cerevisiae*) (SEC14L1, Accession NM\_003003) is another VGAM538 host target gene. SEC14L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEC14L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC14L1 BINDING SITE, designated SEQ ID:8902, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23758] Another function of VGAM538 is therefore inhibition of SEC14-like 1 (*S. cerevisiae*) (SEC14L1, Accession

NM\_003003). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEC14L1. Sp2 Transcription Factor (SP2, Accession NM\_003110) is another VGAM538 host target gene. SP2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SP2 BINDING SITE, designated SEQ ID:9081, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23759] Another function of VGAM538 is therefore inhibition of Sp2 Transcription Factor (SP2, Accession NM\_003110). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SP2. SFRS Protein Kinase 1 (SRPK1, Accession NM\_003137) is another VGAM538 host target gene. SRPK1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SRPK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2

illustrates the complementarity of the nucleotide sequences of SRPK1 BINDING SITE, designated SEQ ID:9110, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23760] Another function of VGAM538 is therefore inhibition of SFRS Protein Kinase 1 (SRPK1, Accession NM\_003137). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRPK1. LOC134266 (Accession XM\_059701) is another VGAM538 host target gene. LOC134266 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC134266, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC134266 BINDING SITE, designated SEQ ID:37072, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23761] Another function of VGAM538 is therefore inhibition of LOC134266 (Accession XM\_059701). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC134266. LOC142972 (Accession XM\_036593) is an-



other VGAM538 host target gene. LOC142972 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC142972, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC142972 BINDING SITE, designated SEQ ID:32478, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23762] Another function of VGAM538 is therefore inhibition of LOC142972 (Accession XM\_036593). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC142972. LOC145439 (Accession XM\_085144) is another VGAM538 host target gene. LOC145439 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145439, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145439 BINDING SITE, designated SEQ ID:37864, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23763] Another function of VGAM538 is therefore inhibition of LOC145439 (Accession XM\_085144). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145439. LOC147165 (Accession XM\_097205) is another VGAM538 host target gene. LOC147165 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147165, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147165 BINDING SITE, designated SEQ ID:40814, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23764] Another function of VGAM538 is therefore inhibition of LOC147165 (Accession XM\_097205). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147165. LOC199232 (Accession XM\_114336) is another VGAM538 host target gene. LOC199232 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199232, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199232 BINDING SITE, designated SEQ ID:42879, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23765] Another function of VGAM538 is therefore inhibition of LOC199232 (Accession XM\_114336). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199232. LOC200609 (Accession XM\_117256) is another VGAM538 host target gene. LOC200609 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200609, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200609 BINDING SITE, designated SEQ ID:43328, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23766] Another function of VGAM538 is therefore inhibition of LOC200609 (Accession XM\_117256). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC200609. LOC200933 (Accession XM\_117294) is another VGAM538 host target gene. LOC200933 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200933, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200933 BINDING SITE, designated SEQ ID:43363, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23767] Another function of VGAM538 is therefore inhibition of LOC200933 (Accession XM\_117294). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200933. LOC253664 (Accession XM\_170673) is another VGAM538 host target gene. LOC253664 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253664, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253664 BINDING SITE, designated SEQ ID:45449, to the nucleotide sequence of VGAM538 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3249.

[23768] Another function of VGAM538 is therefore inhibition of LOC253664 (Accession XM\_170673). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253664. LOC51026 (Accession NM\_016072) is another VGAM538 host target gene. LOC51026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51026 BINDING SITE, designated SEQ ID:18144, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23769] Another function of VGAM538 is therefore inhibition of LOC51026 (Accession NM\_016072). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51026. LOC91351 (Accession XM\_037817) is another VGAM538 host target gene. LOC91351 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91351, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91351 BINDING SITE, designated SEQ ID:32696, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23770] Another function of VGAM538 is therefore inhibition of LOC91351 (Accession XM\_037817). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91351. LOC93512 (Accession XM\_051758) is another VGAM538 host target gene. LOC93512 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93512, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93512 BINDING SITE, designated SEQ ID:35878, to the nucleotide sequence of VGAM538 RNA, herein designated VGAM RNA, also designated SEQ ID:3249.

[23771] Another function of VGAM538 is therefore inhibition of LOC93512 (Accession XM\_051758). Accordingly, utilities of VGAM538 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC93512. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 539 (VGAM539) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23772] VGAM539 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM539 was detected is described hereinabove with reference to Figs. 1–8.

[23773] VGAM539 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Respiratory Syncytial Virus. VGAM539 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23774] VGAM539 gene encodes a VGAM539 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM539 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM539 precursor RNA is designated SEQ

ID:525, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:525 is located at position 10613 relative to the genome of Bovine Respiratory Syncytial Virus.

[23775] VGAM539 precursor RNA folds onto itself, forming VGAM539 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23776] An enzyme complex designated DICER COMPLEX, `dices` the VGAM539 folded precursor RNA into VGAM539 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 56%) nucleotide sequence of VGAM539 RNA is designated SEQ ID:3250, and is provided hereinbelow with reference to the sequence



listing part.

[23777] VGAM539 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM539 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM539 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23778] VGAM539 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM539 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM539 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM539 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM539 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23779] The complementary binding of VGAM539 RNA, herein designated VGAM RNA, to host target binding sites on VGAM539 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM539 host target RNA into VGAM539 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23780] It is appreciated that VGAM539 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM539 host target genes. The mRNA of each one of this plurality of VGAM539 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM539 RNA, herein designated VGAM

RNA, and which when bound by VGAM539 RNA causes inhibition of translation of respective one or more VGAM539 host target proteins.

[23781] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM539 gene, herein designated VGAM GENE, on one or more VGAM539 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23782] It is yet further appreciated that a function of VGAM539 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM539 include diagnosis, prevention and treatment of viral infection by Bovine Respiratory Syncytial Virus. Specific functions, and accordingly utilities, of VGAM539 correlate with, and may be deduced from, the identity of the host target genes which VGAM539 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23783] Nucleotide sequences of the VGAM539 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM539 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM539 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM539 are further described hereinbelow with reference to Table 1.

[23784] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM539 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM539 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23785] As mentioned hereinabove with reference to Fig. 1, a function of VGAM539 gene, herein designated VGAM is

inhibition of expression of VGAM539 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM539 correlate with, and may be deduced from, the identity of the target genes which VGAM539 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23786] Cadherin 6, Type 2, K-cadherin (fetal kidney) (CDH6, Accession NM\_004932) is a VGAM539 host target gene. CDH6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDH6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDH6 BINDING SITE, designated SEQ ID:11371, to the nucleotide sequence of VGAM539 RNA, herein designated VGAM RNA, also designated SEQ ID:3250.

[23787] A function of VGAM539 is therefore inhibition of Cadherin 6, Type 2, K-cadherin (fetal kidney) (CDH6, Accession NM\_004932), a gene which is a calcium dependent cell adhesion protein. Accordingly, utilities of VGAM539 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH6. The function of CDH6 and its association with various diseases and clini-

cal conditions, has been established by previous studies, as described hereinabove with reference to VGAM60. Gamma-aminobutyric Acid (GABA) A Receptor, Epsilon (GABRE, Accession NM\_004961) is another VGAM539 host target gene. GABRE BINDING SITE1 through GABRE BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GABRE, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GABRE BINDING SITE1 through GABRE BINDING SITE4, designated SEQ ID:11406, SEQ ID:22508, SEQ ID:22512 and SEQ ID:22527 respectively, to the nucleotide sequence of VGAM539 RNA, herein designated VGAM RNA, also designated SEQ ID:3250.

[23788] Another function of VGAM539 is therefore inhibition of Gamma-aminobutyric Acid (GABA) A Receptor, Epsilon (GABRE, Accession NM\_004961), a gene which mediates neuronal inhibition by binding to the gaba/benzodiazepine receptor and opening an integral chloride channel. Accordingly, utilities of VGAM539 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GABRE. The function of GABRE

and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM259. Pim-2 Oncogene (PIM2, Accession XM\_010208) is another VGAM539 host target gene. PIM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIM2 BINDING SITE, designated SEQ ID:30132, to the nucleotide sequence of VGAM539 RNA, herein designated VGAM RNA, also designated SEQ ID:3250.

[23789] Another function of VGAM539 is therefore inhibition of Pim-2 Oncogene (PIM2, Accession XM\_010208). Accordingly, utilities of VGAM539 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIM2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 540 (VGAM540) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes

is known in the art.

[23790] VGAM540 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM540 was detected is described hereinabove with reference to Figs. 1–8.

[23791] VGAM540 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Respiratory Syncytial Virus. VGAM540 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23792] VGAM540 gene encodes a VGAM540 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM540 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM540 precursor RNA is designated SEQ ID:526, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:526 is located at position 14011 relative to the genome of Bovine Respiratory Syncytial Virus.

[23793] VGAM540 precursor RNA folds onto itself, forming VGAM540 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional



`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[23794] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM540 folded precursor RNA into VGAM540 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 74%) nucleotide se-  
quence of VGAM540 RNA is designated SEQ ID:3251, and  
is provided hereinbelow with reference to the sequence  
listing part.

[23795] VGAM540 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM540 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM540 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[23796] VGAM540 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM540 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM540 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM540 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM540 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[23797] The complementary binding of VGAM540 RNA, herein designated VGAM RNA, to host target binding sites on VGAM540 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM540 host target RNA into VGAM540 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23798] It is appreciated that VGAM540 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM540 host target genes. The mRNA of each one of this plurality of VGAM540 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM540 RNA, herein designated VGAM RNA, and which when bound by VGAM540 RNA causes inhibition of translation of respective one or more VGAM540 host target proteins.

[23799] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM540 gene, herein designated VGAM GENE, on one or

more VGAM540 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23800] It is yet further appreciated that a function of VGAM540 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM540 include diagnosis, prevention and treatment of viral infection by Bovine Respiratory Syncytial Virus. Specific functions, and accordingly utilities, of VGAM540 correlate with, and may be deduced from, the identity of the host target genes which VGAM540 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [23801] Nucleotide sequences of the VGAM540 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM540 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM540 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM540 are further described hereinbelow with reference to Table 1.
- [23802] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM540 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM540 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [23803] As mentioned hereinabove with reference to Fig. 1, a function of VGAM540 gene, herein designated VGAM is inhibition of expression of VGAM540 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM540 correlate with, and may be deduced from, the identity of the target genes which VGAM540 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [23804] NCK Adaptor Protein 1 (NCK1, Accession NM\_006153) is a

VGAM540 host target gene. NCK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCK1 BINDING SITE, designated SEQ ID:12809, to the nucleotide sequence of VGAM540 RNA, herein designated VGAM RNA, also designated SEQ ID:3251.

[23805] A function of VGAM540 is therefore inhibition of NCK Adaptor Protein 1 (NCK1, Accession NM\_006153). Accordingly, utilities of VGAM540 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCK1. Oxysterol Binding Protein-like 11 (OSBPL11, Accession NM\_022776) is another VGAM540 host target gene. OSBPL11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OSBPL11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSBPL11 BINDING SITE, designated SEQ ID:23046, to the nucleotide sequence of VGAM540 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3251.

[23806] Another function of VGAM540 is therefore inhibition of Oxysterol Binding Protein-like 11 (OSBPL11, Accession NM\_022776). Accordingly, utilities of VGAM540 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OSBPL11. Thioesterase, Adipose Associated (THEA, Accession XM\_038922) is another VGAM540 host target gene. THEA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by THEA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of THEA BINDING SITE, designated SEQ ID:32948, to the nucleotide sequence of VGAM540 RNA, herein designated VGAM RNA, also designated SEQ ID:3251.

[23807] Another function of VGAM540 is therefore inhibition of Thioesterase, Adipose Associated (THEA, Accession XM\_038922). Accordingly, utilities of VGAM540 include diagnosis, prevention and treatment of diseases and clinical conditions associated with THEA. LOC199796 (Accession XM\_058994) is another VGAM540 host target gene. LOC199796 BINDING SITE is HOST TARGET binding

site found in the 5' untranslated region of mRNA encoded by LOC199796, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199796 BINDING SITE, designated SEQ ID:36805, to the nucleotide sequence of VGAM540 RNA, herein designated VGAM RNA, also designated SEQ ID:3251.

[23808] Another function of VGAM540 is therefore inhibition of LOC199796 (Accession XM\_058994). Accordingly, utilities of VGAM540 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199796. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 541 (VGAM541) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23809] VGAM541 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM541 was detected is described hereinabove with reference to Figs. 1-8.



[23810] VGAM541 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Respiratory Syncytial Virus. VGAM541 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23811] VGAM541 gene encodes a VGAM541 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM541 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM541 precursor RNA is designated SEQ ID:527, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:527 is located at position 14726 relative to the genome of Bovine Respiratory Syncytial Virus.

[23812] VGAM541 precursor RNA folds onto itself, forming VGAM541 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[23813] An enzyme complex designated DICER COMPLEX, `dices` the VGAM541 folded precursor RNA into VGAM541 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM541 RNA is designated SEQ ID:3252, and is provided hereinbelow with reference to the sequence listing part.

[23814] VGAM541 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM541 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM541 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23815] VGAM541 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM541 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM541 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM541 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM541 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23816] The complementary binding of VGAM541 RNA, herein designated VGAM RNA, to host target binding sites on VGAM541 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM541 host target RNA into VGAM541 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23817] It is appreciated that VGAM541 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM541 host target genes. The mRNA of each one of this plurality of VGAM541 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM541 RNA, herein designated VGAM RNA, and which when bound by VGAM541 RNA causes inhibition of translation of respective one or more VGAM541 host target proteins.

[23818] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM541 gene, herein designated VGAM GENE, on one or more VGAM541 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23819] It is yet further appreciated that a function of VGAM541 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM541 include diagnosis, prevention and treatment of viral infection by Bovine Respiratory Syncytial Virus. Specific functions, and accordingly utilities, of VGAM541 correlate with, and may be deduced from, the identity of the host target genes which VGAM541 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23820] Nucleotide sequences of the VGAM541 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM541 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM541 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM541 are further described hereinbelow with reference to Table 1.

[23821] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM541 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM541 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23822] As mentioned hereinabove with reference to Fig. 1, a function of VGAM541 gene, herein designated VGAM is inhibition of expression of VGAM541 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM541 correlate with, and may be deduced from, the identity of the target genes which VGAM541 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23823] HSA249128 (Accession NM\_017583) is a VGAM541 host target gene. HSA249128 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSA249128, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of HSA249128 BINDING SITE, designated SEQ ID:19023, to the nucleotide sequence of VGAM541 RNA, herein designated VGAM RNA, also designated SEQ ID:3252.

[23824] A function of VGAM541 is therefore inhibition of HSA249128 (Accession NM\_017583). Accordingly, utilities of VGAM541 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSA249128. KIAA1005 (Accession XM\_051197) is another VGAM541 host target gene. KIAA1005 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1005, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1005 BINDING SITE, designated SEQ ID:35779, to the nucleotide sequence of VGAM541 RNA, herein designated VGAM RNA, also designated SEQ ID:3252.

[23825] Another function of VGAM541 is therefore inhibition of KIAA1005 (Accession XM\_051197). Accordingly, utilities of VGAM541 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1005. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 542 (VGAM542) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23826] VGAM542 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM542 was detected is described hereinabove with reference to Figs. 1–8.

[23827] VGAM542 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Melanoplus Sanguinipes Entomopoxvirus. VGAM542 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23828] VGAM542 gene encodes a VGAM542 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM542 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM542 precursor RNA is designated SEQ ID:528, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:528 is



located at position 229631 relative to the genome of *Melanoplus Sanguinipes* Entomopoxvirus.

[23829] VGAM542 precursor RNA folds onto itself, forming VGAM542 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23830] An enzyme complex designated DICER COMPLEX, `dices` the VGAM542 folded precursor RNA into VGAM542 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM542 RNA is designated SEQ ID:3253, and is provided hereinbelow with reference to the sequence listing part.

[23831] VGAM542 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM542 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM542 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[23832] VGAM542 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM542 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM542 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM542 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM542 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23833] The complementary binding of VGAM542 RNA, herein designated VGAM RNA, to host target binding sites on VGAM542 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM542 host target RNA into VGAM542 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23834] It is appreciated that VGAM542 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM542 host target genes. The mRNA of each one of this plurality of VGAM542 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM542 RNA, herein designated VGAM RNA, and which when bound by VGAM542 RNA causes inhibition of translation of respective one or more VGAM542

host target proteins.

[23835] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM542 gene, herein designated VGAM GENE, on one or more VGAM542 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23836] It is yet further appreciated that a function of VGAM542 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM542 include diagnosis, prevention and treatment of viral infection by Melanoplus Sanguinipes En-

tomopoxvirus. Specific functions, and accordingly utilities, of VGAM542 correlate with, and may be deduced from, the identity of the host target genes which VGAM542 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23837] Nucleotide sequences of the VGAM542 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM542 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM542 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM542 are further described hereinbelow with reference to Table 1.

[23838] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM542 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM542 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23839] As mentioned hereinabove with reference to Fig. 1, a function of VGAM542 gene, herein designated VGAM is inhibition of expression of VGAM542 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM542 correlate with, and may be deduced from, the identity of the target genes which VGAM542 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23840] Endothelin Receptor Type A (EDNRA, Accession XM\_034331) is a VGAM542 host target gene. EDNRA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EDNRA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EDNRA BINDING SITE, designated SEQ ID:32060, to the nucleotide sequence of VGAM542 RNA, herein designated VGAM RNA, also designated SEQ ID:3253.

[23841] A function of VGAM542 is therefore inhibition of Endothelin Receptor Type A (EDNRA, Accession XM\_034331), a gene which binds endothelins, and induces intracellular calcium flux and arachidonic acid accumulation. Accordingly, utilities of VGAM542 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EDNRA. The function of EDNRA and its association with various diseases and clinical conditions, has been established by previous studies, as described here-

in above with reference to VGAM441. Fukuyama Type Congenital Muscular Dystrophy (fukutin) (FCMD, Accession NM\_006731) is another VGAM542 host target gene. FCMD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FCMD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FCMD BINDING SITE, designated SEQ ID:13571, to the nucleotide sequence of VGAM542 RNA, herein designated VGAM RNA, also designated SEQ ID:3253.

[23842] Another function of VGAM542 is therefore inhibition of Fukuyama Type Congenital Muscular Dystrophy (fukutin) (FCMD, Accession NM\_006731). Accordingly, utilities of VGAM542 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FCMD. Inhibitor of Growth Family, Member 1 (ING1, Accession NM\_005537) is another VGAM542 host target gene. ING1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ING1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

ING1 BINDING SITE, designated SEQ ID:12060, to the nucleotide sequence of VGAM542 RNA, herein designated VGAM RNA, also designated SEQ ID:3253.

[23843] Another function of VGAM542 is therefore inhibition of Inhibitor of Growth Family, Member 1 (ING1, Accession NM\_005537), a gene which acts as a potent growth regulator in normal and in established cells. Accordingly, utilities of VGAM542 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ING1. The function of ING1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM170.DKFZP434C1715 (Accession XM\_098421) is another VGAM542 host target gene. DKFZP434C1715 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434C1715, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434C1715 BINDING SITE, designated SEQ ID:41671, to the nucleotide sequence of VGAM542 RNA, herein designated VGAM RNA, also designated SEQ ID:3253.



[23844] Another function of VGAM542 is therefore inhibition of DKFZP434C1715 (Accession XM\_098421). Accordingly, utilities of VGAM542 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434C1715. Oxysterol Binding Protein-like 1A (OSBPL1A, Accession NM\_080597) is another VGAM542 host target gene. OSBPL1A BINDING SITE1 through OSBPL1A BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by OSBPL1A, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSBPL1A BINDING SITE1 through OSBPL1A BINDING SITE3, designated SEQ ID:27906, SEQ ID:28423 and SEQ ID:19771 respectively, to the nucleotide sequence of VGAM542 RNA, herein designated VGAM RNA, also designated SEQ ID:3253.

[23845] Another function of VGAM542 is therefore inhibition of Oxysterol Binding Protein-like 1A (OSBPL1A, Accession NM\_080597). Accordingly, utilities of VGAM542 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OSBPL1A. LOC220038 (Accession XM\_166257) is another VGAM542 host target

gene. LOC220038 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220038 BINDING SITE, designated SEQ ID:44079, to the nucleotide sequence of VGAM542 RNA, herein designated VGAM RNA, also designated SEQ ID:3253.

[23846] Another function of VGAM542 is therefore inhibition of LOC220038 (Accession XM\_166257). Accordingly, utilities of VGAM542 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220038. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 543 (VGAM543) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23847] VGAM543 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM543 was detected is described

hereinabove with reference to Figs. 1–8.

[23848] VGAM543 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Melanoplus Sanguinipes Entomopoxvirus. VGAM543 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23849] VGAM543 gene encodes a VGAM543 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM543 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM543 precursor RNA is designated SEQ ID:529, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:529 is located at position 179507 relative to the genome of Melanoplus Sanguinipes Entomopoxvirus.

[23850] VGAM543 precursor RNA folds onto itself, forming VGAM543 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[23851] An enzyme complex designated DICER COMPLEX, `dices` the VGAM543 folded precursor RNA into VGAM543 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM543 RNA is designated SEQ ID:3254, and is provided hereinbelow with reference to the sequence listing part.

[23852] VGAM543 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM543 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM543 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23853] VGAM543 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM543 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM543 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM543 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM543 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23854] The complementary binding of VGAM543 RNA, herein designated VGAM RNA, to host target binding sites on VGAM543 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM543 host target RNA into VGAM543 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23855] It is appreciated that VGAM543 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM543 host target genes. The mRNA of each one of this plurality of VGAM543 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM543 RNA, herein designated VGAM RNA, and which when bound by VGAM543 RNA causes inhibition of translation of respective one or more VGAM543 host target proteins.

[23856] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM543 gene, herein designated VGAM GENE, on one or more VGAM543 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23857] It is yet further appreciated that a function of VGAM543 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of viral infection by Melanoplus Sanguinipes Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM543 correlate with, and may be deduced from, the identity of the host target genes which VGAM543 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23858] Nucleotide sequences of the VGAM543 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM543 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM543 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM543 are further described hereinbelow with reference to Table 1.

[23859] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM543 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM543 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23860] As mentioned hereinabove with reference to Fig. 1, a function of VGAM543 gene, herein designated VGAM is inhibition of expression of VGAM543 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM543 correlate with, and may be deduced from, the identity of the target genes which VGAM543 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23861] C1D (Accession NM\_006333) is a VGAM543 host target gene. C1D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-



ble 2 illustrates the complementarity of the nucleotide sequences of C1D BINDING SITE, designated SEQ ID:13031, to the nucleotide sequence of VGAM543 RNA, herein designated VGAM RNA, also designated SEQ ID:3254.

[23862] A function of VGAM543 is therefore inhibition of C1D (Accession NM\_006333), a gene which is similar to murine C1D and may be a component of nuclear hormone receptor complexes. Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1D. The function of C1D and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM78.Serum/glucocorticoid Regulated Kinase (SGK, Accession NM\_005627) is another VGAM543 host target gene. SGK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SGK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SGK BINDING SITE, designated SEQ ID:12139, to the nucleotide sequence of VGAM543 RNA, herein designated VGAM RNA, also designated SEQ ID:3254.

[23863] Another function of VGAM543 is therefore inhibition of Serum/glucocorticoid Regulated Kinase (SGK, Accession NM\_005627), a gene which Serine/threonine kinase. Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SGK. The function of SGK has been established by previous studies. Transforming growth factor-beta (TGFB1; 190180) participates in the pathophysiology of diabetic complications. TGF-beta stimulates the expression of SGK. Lang et al. (2000) demonstrated markedly enhanced transcription of SGK in diabetic nephropathy, with particularly high expression in mesangial cells, interstitial cells, and cells in the thick ascending limbs of the loop of Henle and distal tubules. The enhanced SGK transcription, which results from excessive extracellular glucose concentrations, stimulates renal tubular Na(+) transport. These observations disclosed an additional element in the pathophysiology of diabetic nephropathy. Animal model experiments lend further support to the function of SGK. Using differential display PCR, Tsai et al. (2002) identified 98 cDNA fragments from the rat dorsal hippocampus that were expressed differentially between the fast learners and slow learners in the

water maze learning task. One of these cDNA fragments came from the Sgk gene. Northern blot analysis showed that Sgk mRNA levels were approximately 4-fold higher in the hippocampus of fast learners than slow learners. In situ hybridization results indicated that Sgk mRNA levels were increased markedly in the CA1, CA3, and dentate gyrus of the hippocampus of fast learners. Transient transfection of Sgk mutant DNA to the CA1 area of the hippocampus impaired water maze performance in rats, whereas transfection of Sgk wildtype DNA facilitated it.

[23864] It is appreciated that the abovementioned animal model for SGK is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[23865] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23866] Lang, F.; Klingel, K.; Wagner, C. A.; Stegen, C.; Warntges, S.; Friedrich, B.; Lanzendorfer, M.; Melzig, J.; Moschen, I.; Steuer, S.; Waldegger, S.; Sauter, M.; and 9 others : De-ranged transcriptional regulation of cell-volume-sensitive kinase hSGK in diabetic nephropathy. Proc. Nat. Acad. Sci. 97: 8157–8162, 2000. ; and

[23867] Tsai, K. J.; Chen, S. K.; Ma, Y. L.; Hsu, W. L.; Lee, E. H. Y. :  
sgk, a primary glucocorticoid-induced gene, facilitates  
memory consolidation of spatial learning in rats. Proc.  
Nat. Acad.

[23868] Further studies establishing the function and utilities of  
SGK are found in John Hopkins OMIM database record ID  
602958, and in cited publications numbered 2503,  
8644-864 and 8474-8475 listed in the bibliography sec-  
tion hereinbelow, which are also hereby incorporated by  
reference. Chromosome 12 Open Reading Frame 22  
(C12orf22, Accession NM\_030809) is another VGAM543  
host target gene. C12orf22 BINDING SITE is HOST TARGET  
binding site found in the 3' untranslated region of mRNA  
encoded by C12orf22, corresponding to a HOST TARGET  
binding site such as BINDING SITE I, BINDING SITE II or  
BINDING SITE III. Table 2 illustrates the complementarity  
of the nucleotide sequences of C12orf22 BINDING SITE,  
designated SEQ ID:25130, to the nucleotide sequence of  
VGAM543 RNA, herein designated VGAM RNA, also desig-  
nated SEQ ID:3254.

[23869] Another function of VGAM543 is therefore inhibition of  
Chromosome 12 Open Reading Frame 22 (C12orf22, Ac-  
cession NM\_030809). Accordingly, utilities of VGAM543

include diagnosis, prevention and treatment of diseases and clinical conditions associated with C12orf22. GG2-1 (Accession NM\_014350) is another VGAM543 host target gene. GG2-1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GG2-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GG2-1 BINDING SITE, designated SEQ ID:15678, to the nucleotide sequence of VGAM543 RNA, herein designated VGAM RNA, also designated SEQ ID:3254.

[23870] Another function of VGAM543 is therefore inhibition of GG2-1 (Accession NM\_014350). Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GG2-1. HT008 (Accession XM\_008246) is another VGAM543 host target gene. HT008 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HT008, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HT008 BINDING SITE, designated SEQ

ID:30072, to the nucleotide sequence of VGAM543 RNA, herein designated VGAM RNA, also designated SEQ ID:3254.

[23871] Another function of VGAM543 is therefore inhibition of HT008 (Accession XM\_008246). Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HT008. KIAA0820 (Accession XM\_044463) is another VGAM543 host target gene. KIAA0820 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0820, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0820 BINDING SITE, designated SEQ ID:34218, to the nucleotide sequence of VGAM543 RNA, herein designated VGAM RNA, also designated SEQ ID:3254.

[23872] Another function of VGAM543 is therefore inhibition of KIAA0820 (Accession XM\_044463). Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0820. T-cell Leukemia/lymphoma 6 (TCL6, Accession NM\_014418) is another VGAM543 host target gene. TCL6

BINDING SITE1 and TCL6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TCL6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCL6 BINDING SITE1 and TCL6 BINDING SITE2, designated SEQ ID:15766 and SEQ ID:21760 respectively, to the nucleotide sequence of VGAM543 RNA, herein designated VGAM RNA, also designated SEQ ID:3254.

[23873] Another function of VGAM543 is therefore inhibition of T-cell Leukemia/lymphoma 6 (TCL6, Accession NM\_014418). Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCL6. LOC154792 (Accession XM\_098608) is another VGAM543 host target gene. LOC154792 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154792, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154792 BINDING SITE, designated SEQ ID:41728, to the nucleotide sequence of

VGAM543 RNA, herein designated VGAM RNA, also designated SEQ ID:3254.

[23874] Another function of VGAM543 is therefore inhibition of LOC154792 (Accession XM\_098608). Accordingly, utilities of VGAM543 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154792. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 544 (VGAM544) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23875] VGAM544 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM544 was detected is described hereinabove with reference to Figs. 1–8.

[23876] VGAM544 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Infectious Spleen and Kidney Necrosis Virus. VGAM544 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23877] VGAM544 gene encodes a VGAM544 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM544 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM544 precursor RNA is designated SEQ ID:530, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:530 is located at position 22231 relative to the genome of Infectious Spleen and Kidney Necrosis Virus.

[23878] VGAM544 precursor RNA folds onto itself, forming VGAM544 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23879] An enzyme complex designated DICER COMPLEX, `dices` the VGAM544 folded precursor RNA into VGAM544 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM544 RNA is designated SEQ ID:3255, and is provided hereinbelow with reference to the sequence listing part.

[23880] VGAM544 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM544 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM544 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[23881] VGAM544 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM544 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM544 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM544 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM544 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23882] The complementary binding of VGAM544 RNA, herein designated VGAM RNA, to host target binding sites on VGAM544 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM544 host target RNA into VGAM544 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23883] It is appreciated that VGAM544 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM544 host target genes. The mRNA of each one of this plurality of VGAM544 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM544 RNA, herein designated VGAM RNA, and which when bound by VGAM544 RNA causes inhibition of translation of respective one or more VGAM544 host target proteins.

[23884] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM544 gene, herein designated VGAM GENE, on one or more VGAM544 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[23885] It is yet further appreciated that a function of VGAM544 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM544 include diagnosis, prevention and treatment of viral infection by Infectious Spleen and Kidney Necrosis Virus. Specific functions, and accordingly utilities, of VGAM544 correlate with, and may be deduced from, the identity of the host target genes which VGAM544 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23886] Nucleotide sequences of the VGAM544 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM544 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM544 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM544 are further described hereinbelow with reference to Table 1.

[23887] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM544 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM544 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23888] As mentioned hereinabove with reference to Fig. 1, a function of VGAM544 gene, herein designated VGAM is inhibition of expression of VGAM544 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM544 correlate with, and may be deduced from, the identity of the target genes which VGAM544 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23889] PDX1 (Accession NM\_003477) is a VGAM544 host target gene. PDX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDX1 BINDING SITE, designated SEQ ID:9547, to the nucleotide sequence of VGAM544 RNA, herein designated VGAM RNA, also designated SEQ ID:3255.

[23890] A function of VGAM544 is therefore inhibition of PDX1 (Accession NM\_003477). Accordingly, utilities of VGAM544 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PDX1.

S164 (Accession XM\_027330) is another VGAM544 host target gene. S164 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by S164, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of S164 BINDING SITE, designated SEQ ID:30483, to the nucleotide sequence of VGAM544 RNA, herein designated VGAM RNA, also designated SEQ ID:3255.

[23891] Another function of VGAM544 is therefore inhibition of S164 (Accession XM\_027330). Accordingly, utilities of VGAM544 include diagnosis, prevention and treatment of diseases and clinical conditions associated with S164. LOC153338 (Accession XM\_098361) is another VGAM544 host target gene. LOC153338 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153338, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153338 BINDING SITE, designated SEQ ID:41610, to the nucleotide se-

quence of VGAM544 RNA, herein designated VGAM RNA, also designated SEQ ID:3255.

[23892] Another function of VGAM544 is therefore inhibition of LOC153338 (Accession XM\_098361). Accordingly, utilities of VGAM544 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153338. LOC220936 (Accession XM\_166137) is another VGAM544 host target gene. LOC220936 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220936, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220936 BINDING SITE, designated SEQ ID:43930, to the nucleotide sequence of VGAM544 RNA, herein designated VGAM RNA, also designated SEQ ID:3255.

[23893] Another function of VGAM544 is therefore inhibition of LOC220936 (Accession XM\_166137). Accordingly, utilities of VGAM544 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220936. LOC92973 (Accession XM\_048529) is another VGAM544 host target gene. LOC92973 BINDING SITE is HOST TARGET binding site found in the 5' un-



translated region of mRNA encoded by LOC92973, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92973 BINDING SITE, designated SEQ ID:35184, to the nucleotide sequence of VGAM544 RNA, herein designated VGAM RNA, also designated SEQ ID:3255.

[23894] Another function of VGAM544 is therefore inhibition of LOC92973 (Accession XM\_048529). Accordingly, utilities of VGAM544 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92973. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 545 (VGAM545) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23895] VGAM545 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM545 was detected is described hereinabove with reference to Figs. 1–8.

[23896] VGAM545 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Melanoplus Sanguinipes Entomopoxvirus. VGAM545 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23897] VGAM545 gene encodes a VGAM545 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM545 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM545 precursor RNA is designated SEQ ID:531, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:531 is located at position 205892 relative to the genome of Melanoplus Sanguinipes Entomopoxvirus.

[23898] VGAM545 precursor RNA folds onto itself, forming VGAM545 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23899] An enzyme complex designated DICER COMPLEX, `dices` the VGAM545 folded precursor RNA into VGAM545 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 52%) nucleotide sequence of VGAM545 RNA is designated SEQ ID:3256, and is provided hereinbelow with reference to the sequence listing part.

[23900] VGAM545 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM545 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM545 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23901] VGAM545 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM545 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM545 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM545 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM545 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[23902] The complementary binding of VGAM545 RNA, herein designated VGAM RNA, to host target binding sites on VGAM545 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM545 host tar-

get RNA into VGAM545 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23903] It is appreciated that VGAM545 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM545 host target genes. The mRNA of each one of this plurality of VGAM545 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM545 RNA, herein designated VGAM RNA, and which when bound by VGAM545 RNA causes inhibition of translation of respective one or more VGAM545 host target proteins.

[23904] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM545 gene, herein designated VGAM GENE, on one or more VGAM545 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23905] It is yet further appreciated that a function of VGAM545 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM545 include diagnosis, prevention and treatment of viral infection by Melanoplus Sanguinipes Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM545 correlate with, and may be deduced from, the identity of the host target genes which VGAM545 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23906] Nucleotide sequences of the VGAM545 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM545 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM545 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM545 are further

described hereinbelow with reference to Table 1.

[23907] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM545 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM545 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23908] As mentioned hereinabove with reference to Fig. 1, a function of VGAM545 gene, herein designated VGAM is inhibition of expression of VGAM545 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM545 correlate with, and may be deduced from, the identity of the target genes which VGAM545 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23909] Sirtuin Silent Mating Type Information Regulation 2 Homolog 5 (*S. cerevisiae*) (SIRT5, Accession NM\_012241) is a VGAM545 host target gene. SIRT5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SIRT5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of SIRT5 BINDING SITE, designated SEQ ID:14547, to the nucleotide sequence of VGAM545 RNA, herein designated VGAM RNA, also designated SEQ ID:3256.

[23910] A function of VGAM545 is therefore inhibition of Sirtuin Silent Mating Type Information Regulation 2 Homolog 5 (*S. cerevisiae*) (SIRT5, Accession NM\_012241), a gene which acts as a nad-dependent histone deacetylase; silences transcription at telomeres and the ribosomal dna. Accordingly, utilities of VGAM545 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIRT5. The function of SIRT5 has been established by previous studies. The yeast Sir2 protein (Shore et al., 1984) regulates epigenetic gene silencing and, as a possible antiaging effect, suppresses recombination of rDNA. Studies involving cobB, a bacterial Sir2-like gene, have suggested that Sir2 may encode a pyridine nucleotide transferase. By in silico and PCR-cloning techniques, Frye (1999) obtained cDNA sequences encoding 5 human Sir2-like genes, which they called sirtuin-1 to -5 (SIRT1 to SIRT5). The SIRT1 (OMIM Ref. No. 604479) sequence has the closest homology to the *S. cerevisiae* Sir2 protein, while SIRT4 (OMIM Ref. No.



604482) and SIRT5 more closely resemble prokaryotic sirtuin sequences. PCR analysis showed that the 5 human sirtuins are widely expressed in fetal and adult tissues. Recombinant human SIRT2 (OMIM Ref. No. 604480) was able to cause radioactivity to be transferred from (32P)NAD to bovine serum albumin (BSA). When a conserved histidine within SIRT2 was converted to tyrosine, the mutant recombinant protein was unable to transfer radioactivity from (32P)NAD to BSA. These results suggested that the sirtuins may function via mono-ADP-ribosylation of proteins. Tanny et al. (1999) showed that the yeast Sir2 protein can transfer labeled phosphate from nicotinamide adenine dinucleotide to itself and histones in vitro. A modified form of Sir2, which results from its automodification activity, was specifically recognized by anti-mono-ADP-ribose antibodies, suggesting that Sir2 is an ADP-ribosyltransferase. Mutation of a phylogenetically invariant histidine (his364 to tyr) in Sir2 abolished both its enzymatic activity in vitro and its silencing functions in vivo. However, the mutant protein was associated with chromatin and other silencing factors in a manner similar to wildtype Sir2. These findings suggested that Sir2 contains an ADP-ribosyltransferase activity that

is essential for its silencing function.

[23911] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23912] Frye, R. A. : Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. Biochem. Biophys. Res. Commun. 260: 273-279, 1999. ; and

[23913] Tanny, J. C.; Dowd, G. J.; Huang, J.; Hilz, H.; Moazed, D. : An enzymatic activity in the yeast Sir2 protein that is essential for gene silencing. Cell 99: 735-745, 1999.

[23914] Further studies establishing the function and utilities of SIRT5 are found in John Hopkins OMIM database record ID 604483, and in cited publications numbered 5008, 504 and 5051 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer-

ence. Chromosome 20 Open Reading Frame 106

(C20orf106, Accession NM\_080824) is another VGAM545

host target gene. C20orf106 BINDING SITE is HOST TAR-

GET binding site found in the 3' untranslated region of

mRNA encoded by C20orf106, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf106 BINDING SITE, designated SEQ ID:28090, to the nucleotide sequence of VGAM545 RNA, herein designated VGAM RNA, also designated SEQ ID:3256.

[23915] Another function of VGAM545 is therefore inhibition of Chromosome 20 Open Reading Frame 106 (C20orf106, Accession NM\_080824). Accordingly, utilities of VGAM545 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf106.

LOC151248 (Accession XM\_087143) is another VGAM545 host target gene. LOC151248 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151248, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151248 BINDING SITE, designated SEQ ID:39082, to the nucleotide sequence of VGAM545 RNA, herein designated VGAM RNA, also designated SEQ ID:3256.

[23916] Another function of VGAM545 is therefore inhibition of LOC151248 (Accession XM\_087143). Accordingly, utilities of VGAM545 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC151248. LOC90408 (Accession XM\_031517) is another VGAM545 host target gene. LOC90408 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90408, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90408 BINDING SITE, designated SEQ ID:31393, to the nucleotide sequence of VGAM545 RNA, herein designated VGAM RNA, also designated SEQ ID:3256.

[23917] Another function of VGAM545 is therefore inhibition of LOC90408 (Accession XM\_031517). Accordingly, utilities of VGAM545 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90408. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 546 (VGAM546) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23918] VGAM546 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM546 was detected is described hereinabove with reference to Figs. 1–8.

[23919] VGAM546 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Peanut Stunt Virus.

VGAM546 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23920] VGAM546 gene encodes a VGAM546 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM546 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM546 precursor RNA is designated SEQ ID:532, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:532 is located at position 1857 relative to the genome of Peanut Stunt Virus.

[23921] VGAM546 precursor RNA folds onto itself, forming VGAM546 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23922] An enzyme complex designated DICER COMPLEX, `dices` the VGAM546 folded precursor RNA into VGAM546 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM546 RNA is designated SEQ ID:3257, and is provided hereinbelow with reference to the sequence listing part.

[23923] VGAM546 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM546 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM546 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23924] VGAM546 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM546 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM546 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM546 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM546 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23925] The complementary binding of VGAM546 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM546 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM546 host target RNA into VGAM546 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23926] It is appreciated that VGAM546 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM546 host target genes. The mRNA of each one of this plurality of VGAM546 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM546 RNA, herein designated VGAM RNA, and which when bound by VGAM546 RNA causes inhibition of translation of respective one or more VGAM546 host target proteins.

[23927] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM546 gene, herein designated VGAM GENE, on one or more VGAM546 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other



known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23928] It is yet further appreciated that a function of VGAM546 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM546 include diagnosis, prevention and treatment of viral infection by Peanut Stunt Virus. Specific functions, and accordingly utilities, of VGAM546 correlate with, and may be deduced from, the identity of the host target genes which VGAM546 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23929] Nucleotide sequences of the VGAM546 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM546 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM546 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM546 are further described hereinbelow with reference to Table 1.

[23930] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM546 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM546 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23931] As mentioned hereinabove with reference to Fig. 1, a function of VGAM546 gene, herein designated VGAM is inhibition of expression of VGAM546 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM546 correlate with, and may be deduced from, the identity of the target genes which VGAM546 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23932] Chemokine (C-C motif) Receptor-like 1 (CCRL1, Accession NM\_016557) is a VGAM546 host target gene. CCRL1 BINDING SITE is HOST TARGET binding site found in the

3' untranslated region of mRNA encoded by CCRL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CCRL1 BINDING SITE, designated SEQ ID:18632, to the nucleotide sequence of VGAM546 RNA, herein designated VGAM RNA, also designated SEQ ID:3257.

[23933] A function of VGAM546 is therefore inhibition of Chemokine (C-C motif) Receptor-like 1 (CCRL1, Accession NM\_016557), a gene which is a G protein-coupled receptor that binds chemokines of the CC subfamily, especially MCP-4, ELC (SCYA19) and TECK (SCYA25). Accordingly, utilities of VGAM546 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CCRL1. The function of CCRL1 has been established by previous studies. Chemokine receptors are members of the 7-transmembrane-spanning, G protein-coupled receptor family that recognize small proteins responsible for the directed migration of specific cell types. Depending on the number of amino acids between the first 2 cysteines of their ligands (they may have more than 1 ligand), chemokine receptors are designated CCR (adjacent cysteines), CXCR (1 amino acid between the cysteines), or

CX3CR (3 amino acids between the cysteines). The 'R' designation refers to proteins that not only bind, but also have a signaling function after binding. By searching an EST database for PPR1 homologs, Schweickart et al. (2000) obtained a cDNA encoding CCRL1, which they called CCR11. They initially reported that CCRL1 shares functional similarity to CCR2 (OMIM Ref. No. 601267) because it has a chemotactic response to MCP family chemokines (e.g., MCP2; 602283). However, in an erratum, Schweickart et al. (2000) corrected their functional data and stated that cells expressing CCRL1 do not have a chemotactic response to MCP family chemokines. They confirmed that CCRL1 binds ELC, SLC, and TECK, as reported by Gosling et al. (2000).

[23934] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23935] Schweickart, V. L.; Epp, A.; Raport, C. J.; Gray, P. W. : CCR11 is a functional receptor for the monocyte chemoattractant protein family of chemokines. J. Biol. Chem. 275: 9550–9556, 2000. Note: Erratum: J. Biol. Chem. 276: 856 only, 2001. ; and

[23936] Gosling, J.; Dairaghi, D. J.; Wang, Y.; Hanley, M.; Talbot,

D.; Miao, Z.; Schall, T. J. : Cutting edge: identification of a novel chemokine receptor that binds dendritic cell- and T cel.

[23937] Further studies establishing the function and utilities of CCRL1 are found in John Hopkins OMIM database record ID 606065, and in cited publications numbered 6908–6339 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC200845 (Accession XM\_114305) is another VGAM546 host target gene. LOC200845 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC200845, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200845 BINDING SITE, designated SEQ ID:42862, to the nucleotide sequence of VGAM546 RNA, herein designated VGAM RNA, also designated SEQ ID:3257.

[23938] Another function of VGAM546 is therefore inhibition of LOC200845 (Accession XM\_114305). Accordingly, utilities of VGAM546 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200845. LOC221975 (Accession XM\_166534) is an–

other VGAM546 host target gene. LOC221975 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221975, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221975 BINDING SITE, designated SEQ ID:44497, to the nucleotide sequence of VGAM546 RNA, herein designated VGAM RNA, also designated SEQ ID:3257.

[23939] Another function of VGAM546 is therefore inhibition of LOC221975 (Accession XM\_166534). Accordingly, utilities of VGAM546 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221975. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 547 (VGAM547) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23940] VGAM547 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM547 was detected is described

hereinabove with reference to Figs. 1–8.

[23941] VGAM547 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Peanut Stunt Virus.

VGAM547 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23942] VGAM547 gene encodes a VGAM547 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM547 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM547 precursor RNA is designated SEQ ID:533, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:533 is located at position 1186 relative to the genome of Peanut Stunt Virus.

[23943] VGAM547 precursor RNA folds onto itself, forming VGAM547 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23944] An enzyme complex designated DICER COMPLEX, `dices` the VGAM547 folded precursor RNA into VGAM547 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 66%) nucleotide sequence of VGAM547 RNA is designated SEQ ID:3258, and is provided hereinbelow with reference to the sequence listing part.

[23945] VGAM547 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM547 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM547 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23946] VGAM547 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-



cated in untranslated regions of VGAM547 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM547 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM547 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM547 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23947] The complementary binding of VGAM547 RNA, herein designated VGAM RNA, to host target binding sites on VGAM547 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM547 host target RNA into VGAM547 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23948] It is appreciated that VGAM547 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM547 host target genes. The mRNA of each one of this plurality of VGAM547 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM547 RNA, herein designated VGAM RNA, and which when bound by VGAM547 RNA causes inhibition of translation of respective one or more VGAM547 host target proteins.

[23949] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM547 gene, herein designated VGAM GENE, on one or more VGAM547 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23950] It is yet further appreciated that a function of VGAM547 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM547 include diagnosis, prevention and treatment of viral infection by Peanut Stunt Virus. Specific functions, and accordingly utilities, of VGAM547 correlate with, and may be deduced from, the identity of the host target genes which VGAM547 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23951] Nucleotide sequences of the VGAM547 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM547 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM547 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM547 are further described hereinbelow with reference to Table 1.

[23952] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM547 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM547 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23953] As mentioned hereinabove with reference to Fig. 1, a function of VGAM547 gene, herein designated VGAM is inhibition of expression of VGAM547 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM547 correlate with, and may be deduced from, the identity of the target genes which VGAM547 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23954] Aspartate Beta-hydroxylase (ASPH, Accession NM\_032466) is a VGAM547 host target gene. ASPH BINDING SITE1 and ASPH BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ASPH, corresponding to HOST TARGET binding

sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASPH BINDING SITE1 and ASPH BINDING SITE2, designated SEQ ID:26224 and SEQ ID:26228 respectively, to the nucleotide sequence of VGAM547 RNA, herein designated VGAM RNA, also designated SEQ ID:3258.

[23955] A function of VGAM547 is therefore inhibition of Aspartate Beta-hydroxylase (ASPH, Accession NM\_032466), a gene which specifically hydroxylates the beta carbon of aspartic acid or asparagine residues in certain epidermal growth factor (EGF)-like domains of a number of proteins. Accordingly, utilities of VGAM547 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASPH. The function of ASPH and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM47. Solute Carrier Family 17 (sodium phosphate), Member 4 (SLC17A4, Accession NM\_005495) is another VGAM547 host target gene. SLC17A4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC17A4, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC17A4 BINDING SITE, designated SEQ ID:11998, to the nucleotide sequence of VGAM547 RNA, herein designated VGAM RNA, also designated SEQ ID:3258.

[23956] Another function of VGAM547 is therefore inhibition of Solute Carrier Family 17 (sodium phosphate), Member 4 (SLC17A4, Accession NM\_005495). Accordingly, utilities of VGAM547 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC17A4. Chromosome 20 Open Reading Frame 110 (C20orf110, Accession XM\_086728) is another VGAM547 host target gene. C20orf110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf110 BINDING SITE, designated SEQ ID:38833, to the nucleotide sequence of VGAM547 RNA, herein designated VGAM RNA, also designated SEQ ID:3258.

[23957] Another function of VGAM547 is therefore inhibition of

Chromosome 20 Open Reading Frame 110 (C20orf110, Accession XM\_086728). Accordingly, utilities of VGAM547 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf110. Zinc Finger Protein 323 (ZNF323, Accession NM\_030899) is another VGAM547 host target gene. ZNF323 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF323, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF323 BINDING SITE, designated SEQ ID:25168, to the nucleotide sequence of VGAM547 RNA, herein designated VGAM RNA, also designated SEQ ID:3258.

[23958] Another function of VGAM547 is therefore inhibition of Zinc Finger Protein 323 (ZNF323, Accession NM\_030899). Accordingly, utilities of VGAM547 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF323. LOC149619 (Accession XM\_097690) is another VGAM547 host target gene. LOC149619 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149619, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149619 BINDING SITE, designated SEQ ID:41027, to the nucleotide sequence of VGAM547 RNA, herein designated VGAM RNA, also designated SEQ ID:3258.

[23959] Another function of VGAM547 is therefore inhibition of LOC149619 (Accession XM\_097690). Accordingly, utilities of VGAM547 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149619. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 548 (VGAM548) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23960] VGAM548 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM548 was detected is described hereinabove with reference to Figs. 1–8.

[23961] VGAM548 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Leaf Curl Virus.



VGAM548 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23962] VGAM548 gene encodes a VGAM548 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM548 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM548 precursor RNA is designated SEQ ID:534, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:534 is located at position 462 relative to the genome of Tomato Leaf Curl Virus.

[23963] VGAM548 precursor RNA folds onto itself, forming VGAM548 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23964] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM548 folded precursor RNA into VGAM548 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM548 RNA is designated SEQ ID:3259, and is provided hereinbelow with reference to the sequence listing part.

[23965] VGAM548 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM548 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM548 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[23966] VGAM548 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM548 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM548 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM548 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM548 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[23967] The complementary binding of VGAM548 RNA, herein designated VGAM RNA, to host target binding sites on VGAM548 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM548 host target RNA into VGAM548 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[23968] It is appreciated that VGAM548 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM548 host target genes. The mRNA of each one of this plurality of VGAM548 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM548 RNA, herein designated VGAM RNA, and which when bound by VGAM548 RNA causes inhibition of translation of respective one or more VGAM548 host target proteins.

[23969] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM548 gene, herein designated VGAM GENE, on one or more VGAM548 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[23970] It is yet further appreciated that a function of VGAM548 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of viral infection by Tomato Leaf Curl Virus. Specific functions, and accordingly utilities, of VGAM548 correlate with, and may be deduced from, the identity of the host target genes which VGAM548 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[23971] Nucleotide sequences of the VGAM548 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM548 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM548 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM548 are further described hereinbelow with reference to Table 1.

[23972] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM548 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM548 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[23973] As mentioned hereinabove with reference to Fig. 1, a function of VGAM548 gene, herein designated VGAM is inhibition of expression of VGAM548 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM548 correlate with, and may be deduced from, the identity of the target genes which VGAM548 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[23974] KIAA0857 (Accession XM\_039552) is a VGAM548 host target gene. KIAA0857 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0857, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0857 BINDING SITE, designated SEQ ID:33120, to the nucleotide sequence of

VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23975] A function of VGAM548 is therefore inhibition of KIAA0857 (Accession XM\_039552), a gene which is involved in cytoskeletal organization and cellular growth. Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0857. The function of KIAA0857 has been established by previous studies. RAB11 (see OMIM Ref. No. 604198) is a GTPase that regulates endosomal trafficking to apical plasma membrane domains in polarized epithelial cells. Using protein purification and microsequence analysis, Prekeris et al. (2000) identified a novel RAB11 effector, which they called RIP11. RIP11 is identical to the KIAA0857 open reading frame (Nagase et al., 1998), which encodes a 653-amino acid protein. Northern blot analysis detected 2 major RIP11 transcripts of 4.4 and 6 kb. Both transcripts were enriched in kidney, while other tissues expressed reduced levels of RIP11. Antibodies recognized a protein doublet of 72 kD. RIP11 was found to be enriched in polarized epithelial cells where, like Rab11, it localized to subapical recycling endosomes (AREs) and the apical plasma membrane. Transport assays

demonstrated that RIP11 is important for protein trafficking from AREs to the apical plasma membrane. RIP11 is recruited to AREs by binding to RAB11, as well as through a  $Mg(2+)$ -dependent interaction of its C2 domain with neutral phospholipids. The association of RIP11 with membranes is regulated by a phosphorylation and dephosphorylation cycle. Prekeris et al. (2000) proposed a model whereby the RAB11/RIP11 complex regulates vesicle targeting from the ARE

[23976] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23977] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Hiro-sawa, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Oharo, O. : Prediction of the coding sequences of unidentified human genes. XII. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. DNA Res. 5: 355–364, 1998. ; and

[23978] Prekeris, R.; Klumperman, J.; Scheller, R. H. : A Rab11/Rip11 protein complex regulates apical membrane trafficking via recycling endosomes. Molec. Cell 6: 1437–1448, 2000.

[23979] Further studies establishing the function and utilities of



KIAA0857 are found in John Hopkins OMIM database record ID 605536, and in cited publications numbered 2011 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Vasoactive Intestinal Peptide Receptor 1 (VIPR1, Accession NM\_004624) is another VGAM548 host target gene. VIPR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VIPR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VIPR1 BINDING SITE, designated SEQ ID:10992, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23980] Another function of VGAM548 is therefore inhibition of Vasoactive Intestinal Peptide Receptor 1 (VIPR1, Accession NM\_004624), a gene which binds vip and is mediated by g proteins which activate adenylyl cyclase. Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VIPR1. The function of VIPR1 has been established by previous studies. Vasoactive intestinal peptide (VIP; 192320) is an octacosameric neuroendocrine mediator found pre-

dominantly in cholinergic presynaptic neurons of the central nervous system and in peripheral peptidergic neurons innervating diverse tissues. Of the many neuroendocrine peptides with immunologic functions, VIP is distinguished by its capacity to affect both B and T cells directly. Distinct subsets of neural, respiratory, gastrointestinal, and immune cells bear specific high-affinity receptors for VIP, which are associated with a guanine nucleotide-binding (G) protein capable of activating adenylate cyclase. Libert et al. (1991) obtained 4 new receptors of the G protein-coupled receptor family by selective amplification and cloning from thyroid cDNA. One of these, termed RDC1, was identified as the VIP receptor by Sreedharan et al. (1991). Libert et al. (1991) mapped the VIPR gene to 2q37 by in situ hybridization. Later information made it doubtful that the gene mapped to 2q37 was in fact the VIP receptor gene (Vassart, 1992). The sequence that was designated GPRN1 by Sreedharan et al. (1991) and mapped to 2q37 was found not to bind VIP by Wenger (1993). Sreedharan et al. (1995) isolated an authentic type I VIP receptor gene and by fluorescence in situ hybridization localized it to the 3p22 band in a region associated with small-cell lung cancer. By interspecific backcross analysis,

Hashimoto et al. (1999) mapped the mouse *Vipr1* gene to the distal region of chromosome 9, a region that shows homology of synteny with human chromosome 3p. Sreedharan et al. (1993) cloned a human intestinal VIP receptor gene; the deduced amino acid sequence shares 84% identity with the rat lung VIP receptor. Couvineau et al. (1994) isolated 2 VIPR cDNA clones from a human jejunal epithelial cell cDNA library. One encodes a VIP receptor consisting of 460 amino acids and having 7 putative transmembrane domains, as do other G protein-coupled receptors. The other encodes a 495-amino acid VIP receptor-related protein exhibiting 100% homology with the functional VIP receptor over the 428 amino acids at the C-terminal region, but containing a completely divergent 67-amino acid N-terminal domain. When expressed in COS-7 cells, the second protein did not bind radioiodinated VIP, although it was normally addressed at the plasma membrane as assessed by immunofluorescence studies.

[23981] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[23982] Sreedharan, S. P.; Huang, J.-X.; Cheung, M.-C.; Goetzl, E. J. : Structure, expression, and chromosomal localization of

the type I human vasoactive intestinal peptide receptor gene. Proc. Nat. Acad. Sci. 92: 2939–2943, 1995. ; and

[23983] Couvineau, A.; Rouyer–Fessard, C.; Darmoul, D.; Maoret, J.–J.; Carrero, I.; Ogier–Denis, E.; Laburthe, M. : Human intestinal VIP receptor: cloning and functional expression of two cDNA enc.

[23984] Further studies establishing the function and utilities of VIPR1 are found in John Hopkins OMIM database record ID 192321, and in cited publications numbered 9672–9673, 189, 9674–967 and 9743–9744 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. C16orf5 (Accession NM\_013399) is another VGAM548 host target gene. C16orf5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by C16orf5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C16orf5 BINDING SITE, designated SEQ ID:15053, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23985] Another function of VGAM548 is therefore inhibition of C16orf5 (Accession NM\_013399). Accordingly, utilities of

VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C16orf5. KIAA0427 (Accession NM\_014772) is another VGAM548 host target gene. KIAA0427 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0427, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0427 BINDING SITE, designated SEQ ID:16575, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23986] Another function of VGAM548 is therefore inhibition of KIAA0427 (Accession NM\_014772). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0427. KIAA1163 (Accession XM\_086231) is another VGAM548 host target gene. KIAA1163 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1163, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1163 BINDING SITE, designated SEQ ID:38559, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23987] Another function of VGAM548 is therefore inhibition of KIAA1163 (Accession XM\_086231). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1163. KIAA1889 (Accession XM\_056298) is another VGAM548 host target gene. KIAA1889 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1889, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1889 BINDING SITE, designated SEQ ID:36391, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23988] Another function of VGAM548 is therefore inhibition of KIAA1889 (Accession XM\_056298). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1889. MGC5139 (Accession XM\_058587) is another VGAM548 host target gene. MGC5139 BINDING SITE is

HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC5139, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5139 BINDING SITE, designated SEQ ID:36678, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23989] Another function of VGAM548 is therefore inhibition of MGC5139 (Accession XM\_058587). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5139. PRO2435 (Accession NM\_018527) is another VGAM548 host target gene. PRO2435 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO2435, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2435 BINDING SITE, designated SEQ ID:20602, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23990] Another function of VGAM548 is therefore inhibition of

PRO2435 (Accession NM\_018527). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2435. Three Prime Repair Exonuclease 1 (TREX1, Accession NM\_033627) is another VGAM548 host target gene. TREX1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by TREX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TREX1 BINDING SITE, designated SEQ ID:27338, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23991] Another function of VGAM548 is therefore inhibition of Three Prime Repair Exonuclease 1 (TREX1, Accession NM\_033627). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TREX1. LOC113146 (Accession XM\_053817) is another VGAM548 host target gene. LOC113146 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC113146, corresponding to a HOST TARGET binding



site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC113146 BINDING SITE, designated SEQ ID:36128, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23992] Another function of VGAM548 is therefore inhibition of LOC113146 (Accession XM\_053817). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC113146. LOC90826 (Accession XM\_034321) is another VGAM548 host target gene. LOC90826 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90826 BINDING SITE, designated SEQ ID:32049, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23993] Another function of VGAM548 is therefore inhibition of LOC90826 (Accession XM\_034321). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC90826. LOC92822 (Accession XM\_047520) is another VGAM548 host target gene. LOC92822 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92822, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92822 BINDING SITE, designated SEQ ID:34984, to the nucleotide sequence of VGAM548 RNA, herein designated VGAM RNA, also designated SEQ ID:3259.

[23994] Another function of VGAM548 is therefore inhibition of LOC92822 (Accession XM\_047520). Accordingly, utilities of VGAM548 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92822. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 549 (VGAM549) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[23995] VGAM549 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM549 was detected is described hereinabove with reference to Figs. 1–8.

[23996] VGAM549 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Leishmania RNA Virus 1–1. VGAM549 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[23997] VGAM549 gene encodes a VGAM549 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM549 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM549 precursor RNA is designated SEQ ID:535, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:535 is located at position 1399 relative to the genome of Leishmania RNA Virus 1–1.

[23998] VGAM549 precursor RNA folds onto itself, forming VGAM549 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[23999] An enzyme complex designated DICER COMPLEX, `dices` the VGAM549 folded precursor RNA into VGAM549 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM549 RNA is designated SEQ ID:3260, and is provided hereinbelow with reference to the sequence listing part.

[24000] VGAM549 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM549 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM549 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24001] VGAM549 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM549 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM549 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM549 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM549 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24002] The complementary binding of VGAM549 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM549 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM549 host target RNA into VGAM549 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24003] It is appreciated that VGAM549 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM549 host target genes. The mRNA of each one of this plurality of VGAM549 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM549 RNA, herein designated VGAM RNA, and which when bound by VGAM549 RNA causes inhibition of translation of respective one or more VGAM549 host target proteins.

[24004] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM549 gene, herein designated VGAM GENE, on one or more VGAM549 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24005] It is yet further appreciated that a function of VGAM549 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of viral infection by Leishmania RNA Virus 1-1. Specific functions, and accordingly utilities, of VGAM549 correlate with, and may be deduced from, the identity of the host target genes which VGAM549 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24006] Nucleotide sequences of the VGAM549 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM549 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM549 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM549 are further described hereinbelow with reference to Table 1.

[24007] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM549 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM549 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24008] As mentioned hereinabove with reference to Fig. 1, a function of VGAM549 gene, herein designated VGAM is inhibition of expression of VGAM549 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM549 correlate with, and may be deduced from, the identity of the target genes which VGAM549 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24009] Acyl-Coenzyme A Dehydrogenase, Short/branched Chain (ACADSB, Accession NM\_001609) is a VGAM549 host target gene. ACADSB BINDING SITE is HOST TARGET binding



site found in the 3` untranslated region of mRNA encoded by ACADSB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACADSB BINDING SITE, designated SEQ ID:7312, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24010] A function of VGAM549 is therefore inhibition of Acyl-Coenzyme A Dehydrogenase, Short/branched Chain (ACADSB, Accession NM\_001609). Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACADSB. Arginine Vasopressin Receptor 1A (AVPR1A, Accession NM\_000706) is another VGAM549 host target gene. AVPR1A BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by AVPR1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AVPR1A BINDING SITE, designated SEQ ID:6375, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ

ID:3260.

[24011] Another function of VGAM549 is therefore inhibition of Arginine Vasopressin Receptor 1A (AVPR1A, Accession NM\_000706), a gene which mediates cell contraction and proliferation, platelet aggregation, release of coagulation factor, and glycogenolysis. Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AVPR1A. The function of AVPR1A has been established by previous studies. The antidiuretic hormone vasopressin (OMIM Ref. No. 192340) is a cyclic nonapeptide involved in the control of body fluid osmolality, blood volume, blood pressure, and vascular tone. It acts by binding to G protein-coupled membrane receptors (see OMIM Ref. No. AVPR1B, 600264). One member of this receptor family is AVPR1A, which mediates cell contraction and proliferation, platelet aggregation, release of coagulation factor, and glycogenolysis. AVP action through the V1A receptor is mediated by activating phospholipase C, which in turn stimulates phosphatidylinositol turnover to increase intracellular calcium ion. Morel et al. (1992) cloned the rat hepatocyte V1A receptor. Based on that sequence, Thibonnier et al. (1994) screened a human liver cDNA library. The

cDNA encodes a predicted protein of 418 amino acids with 7 putative transmembrane domains as seen in other G protein-coupled receptors. The protein was 72% identical to the rat sequence and 36% identical to the human V2 receptor (see OMIM Ref. No. 304800). Human oxytocin receptor (OMIM Ref. No. 167055) was 45% similar to AVPR1A. Recombinant V1A was expressed and localized to the cell surface. Birnbaumer (2000) noted that the biologic effects of AVP are mediated by 3 receptor subtypes: the V1A and V1B receptors that activate phospholipases via Gq/11, and the V2 receptor that activates adenylyl cyclase by interacting with GS. Isolation of the cDNAs encoding the V1A and V1B receptor subtypes explained the tissue variability of V1 antagonist binding, whereas identification of the cDNA and gene encoding the V2 receptor provided the information to identify the mutations responsible for X-linked nephrogenic diabetes insipidus (OMIM Ref. No. 304800). Mutations that abrogate the production and/or release of AVP from the pituitary have diabetes insipidus as their most dramatic manifestation, indicating that the maintenance of water homeostasis is the most important physiologic role of this neuropeptide. Animal model experiments lend further support to the func-

tion of AVPR1A. Arginine vasopressin influences male reproductive and social behaviors in several vertebrate taxa through its actions at the V1A receptor in the brain. The neuroanatomic distribution of vasopressin V1A receptors varies greatly between species with different forms of social organization. Young et al. (1999) demonstrated that centrally administered arginine vasopressin increases affiliative behavior in the highly social, monogamous prairie vole, but not in the relatively asocial, promiscuous montane vole. While no significant differences were found in the coding regions of the V1A receptor of the 2 species, the 5-prime flanking region of the V1A gene displayed marked differences between the species. In the prairie vole V1A receptor gene, the 5-prime flanking region contained a 428-bp sequence that is rich in microsatellite DNA. This sequence was not found in the montane vole V1A gene, and sequences on either side of the expansion were contiguous in the montane vole gene. Another monogamous vole, the pine vole, was found to have the same 428-bp sequence in the 5-prime flanking region. Young et al. (1999) generated mice that were transgenic for the prairie vole receptor gene and found that they had a neuroanatomic pattern of receptor binding that was

similar to that of the prairie vole and exhibited increased affiliative behavior after injection with arginine vasopressin. Young et al. (1999) concluded that the pattern of V1A receptor gene expression in the brain may be functionally associated with species-typical social behaviors in male vertebrates.

[24012] It is appreciated that the abovementioned animal model for AVPR1A is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[24013] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24014] Birnbaumer, M. : Vasopressin receptors. TEM 11: 406-410, 2000. ; and

[24015] Young, L. J.; Nilsen, R.; Waymire, K. G.; MacGregor, G. R.; Insel, T. R. : Increased affiliative response to vasopressin in mice expressing the V(1A) receptor from a monogamous vole. Na.

[24016] Further studies establishing the function and utilities of AVPR1A are found in John Hopkins OMIM database record ID 600821, and in cited publications numbered 737 and 7531-7535 listed in the bibliography section hereinbelow,

which are also hereby incorporated by reference. T-cell Acute Lymphocytic Leukemia 1 (TAL1, Accession NM\_003189) is another VGAM549 host target gene. TAL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TAL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAL1 BINDING SITE, designated SEQ ID:9170, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24017] Another function of VGAM549 is therefore inhibition of T-cell Acute Lymphocytic Leukemia 1 (TAL1, Accession NM\_003189), a gene which may help control cell growth and differentiation. Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAL1. The function of TAL1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM172. Cadherin-like 26 (CDH26, Accession NM\_021810) is another VGAM549 host target gene. CDH26 BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by CDH26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDH26 BINDING SITE, designated SEQ ID:22371, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24018] Another function of VGAM549 is therefore inhibition of Cadherin-like 26 (CDH26, Accession NM\_021810). Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH26. FLJ12587 (Accession NM\_022480) is another VGAM549 host target gene. FLJ12587 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12587, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12587 BINDING SITE, designated SEQ ID:22849, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24019] Another function of VGAM549 is therefore inhibition of

FLJ12587 (Accession NM\_022480). Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12587. FLJ20073 (Accession NM\_017654) is another VGAM549 host target gene. FLJ20073 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20073, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20073 BINDING SITE, designated SEQ ID:19163, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24020] Another function of VGAM549 is therefore inhibition of FLJ20073 (Accession NM\_017654). Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20073. MGC15875 (Accession NM\_032921) is another VGAM549 host target gene. MGC15875 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC15875, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-



tarity of the nucleotide sequences of MGC15875 BINDING SITE, designated SEQ ID:26746, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24021] Another function of VGAM549 is therefore inhibition of MGC15875 (Accession NM\_032921). Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15875. MGC2654 (Accession NM\_024109) is another VGAM549 host target gene. MGC2654 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2654, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2654 BINDING SITE, designated SEQ ID:23553, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24022] Another function of VGAM549 is therefore inhibition of MGC2654 (Accession NM\_024109). Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2654. LOC255251 (Accession XM\_171096) is another

VGAM549 host target gene. LOC255251 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255251 BINDING SITE, designated SEQ ID:45907, to the nucleotide sequence of VGAM549 RNA, herein designated VGAM RNA, also designated SEQ ID:3260.

[24023] Another function of VGAM549 is therefore inhibition of LOC255251 (Accession XM\_171096). Accordingly, utilities of VGAM549 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255251. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 550 (VGAM550) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24024] VGAM550 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM550 was detected is described

hereinabove with reference to Figs. 1–8.

[24025] VGAM550 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Leishmania RNA Virus 2–1. VGAM550 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24026] VGAM550 gene encodes a VGAM550 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM550 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM550 precursor RNA is designated SEQ ID:536, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:536 is located at position 4755 relative to the genome of Leishmania RNA Virus 2–1.

[24027] VGAM550 precursor RNA folds onto itself, forming VGAM550 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24028] An enzyme complex designated DICER COMPLEX, `dices` the VGAM550 folded precursor RNA into VGAM550 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM550 RNA is designated SEQ ID:3261, and is provided hereinbelow with reference to the sequence listing part.

[24029] VGAM550 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM550 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM550 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24030] VGAM550 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM550 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM550 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM550 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM550 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24031] The complementary binding of VGAM550 RNA, herein designated VGAM RNA, to host target binding sites on VGAM550 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM550 host target RNA into VGAM550 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24032] It is appreciated that VGAM550 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM550 host target genes. The mRNA of each one of this plurality of VGAM550 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM550 RNA, herein designated VGAM RNA, and which when bound by VGAM550 RNA causes inhibition of translation of respective one or more VGAM550 host target proteins.

[24033] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM550 gene, herein designated VGAM GENE, on one or more VGAM550 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24034] It is yet further appreciated that a function of VGAM550 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of viral infection by Leishmania RNA Virus 2-1. Specific functions, and accordingly utilities, of VGAM550 correlate with, and may be deduced from, the identity of the host target genes which VGAM550 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24035] Nucleotide sequences of the VGAM550 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM550 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM550 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM550 are further described hereinbelow with reference to Table 1.

[24036] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM550 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM550 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24037] As mentioned hereinabove with reference to Fig. 1, a function of VGAM550 gene, herein designated VGAM is inhibition of expression of VGAM550 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM550 correlate with, and may be deduced from, the identity of the target genes which VGAM550 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24038] Carnitine O-octanoyltransferase (CROT, Accession NM\_021151) is a VGAM550 host target gene. CROT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CROT, corresponding to a HOST TARGET binding site such as BINDING



SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CROT BINDING SITE, designated SEQ ID:22124, to the nucleotide sequence of VGAM550 RNA, herein designated VGAM RNA, also designated SEQ ID:3261.

[24039] A function of VGAM550 is therefore inhibition of Carnitine O-octanoyltransferase (CROT, Accession NM\_021151), a gene which CROT plays a crucial role in the beta-oxidation of branched-chain fatty acids including pristanic acid. Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CROT. The function of CROT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM70. Follistatin-like 3 (secreted glycoprotein) (FSTL3, Accession NM\_005860) is another VGAM550 host target gene. FSTL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FSTL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FSTL3 BINDING SITE, designated SEQ ID:12472, to the nucleotide se-

quence of VGAM550 RNA, herein designated VGAM RNA, also designated SEQ ID:3261.

[24040] Another function of VGAM550 is therefore inhibition of Follistatin-like 3 (secreted glycoprotein) (FSTL3, Accession NM\_005860), a gene which is a member of the follistatin-module-protein family. Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FSTL3. The function of FSTL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200. Glutamic-oxaloacetic Transaminase 1, Soluble (aspartate aminotransferase 1) (GOT1, Accession NM\_002079) is another VGAM550 host target gene. GOT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GOT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GOT1 BINDING SITE, designated SEQ ID:7867, to the nucleotide sequence of VGAM550 RNA, herein designated VGAM RNA, also designated SEQ ID:3261.

[24041] Another function of VGAM550 is therefore inhibition of

Glutamic-oxaloacetic Transaminase 1, Soluble (aspartate aminotransferase 1) (GOT1, Accession NM\_002079), a gene which reversibly transfers amino group from aspartate to 2-oxoglutarate to form oxaloacetate and glutamate. Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GOT1. The function of GOT1 has been established by previous studies. Glutamate oxaloacetate transaminase (EC 2.6.1.1) is a ubiquitous pyridoxal phosphate-dependent enzyme which exists in both mitochondrial (OMIM Ref. No. 138150) and cytosolic forms. The enzyme plays an important role in amino acid metabolism and in the urea and tricarboxylic acid cycles. The 2 isoenzymes are homodimeric. In liver about 80% of the enzyme activity is mitochondrial in origin, whereas in serum the enzyme activity is largely cytosolic. Although the mitochondrial and soluble forms of GOT are coded by different chromosomes (according to a rule that has few exceptions; McKusick, 1986), the 2 show close homology in amino acid sequence and were presumably derived from a common ancestral gene (Ford et al., 1980; Doonan et al., 1984). Panteghini (1990) reviewed the clinical usefulness of assays for aspartate aminotransferase (AST)

isoenzymes in serum. By analysis of mouse–human somatic cell hybrids, Creagan et al. (1973) concluded that the structural locus for cytoplasmic glutamate oxaloacetate transaminase is on chromosome 10. Spritz et al. (1979) studied soluble GOT activity in fibroblasts of 2 persons with duplications of the long arm of chromosome 10. Since the 2 differed by only half a band, the authors concluded that the structural locus is on band 10q24. Koch et al. (1981) pointed out that GOT1 and LIPA (OMIM Ref. No. 278000) are also syntenic on chromosome 19 of the mouse. Junien et al. (1982) assigned GOT1 and PGAMA (OMIM Ref. No. 172250) to 10q26.1 (or 10q25.3) by dosage studies. Pol et al. (1988) cloned cDNAs corresponding to human liver cytosolic and mitochondrial aspartate aminotransferase mRNAs. Pol et al. (1989) used these cDNA probes to locate the GOT1 gene in the region 10q24.1–q25.1 by in situ hybridization. Wang et al. (1999) located the GOT1 gene within the critical region for the urofacial syndrome (OMIM Ref. No. 236730), between markers D10S198 and D10S2494, but excluded it as a candidate for that disorder by mutation analysis.

[24042] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [24043] McKusick, V. A. : The morbid anatomy of the human genome: a review of gene mapping in clinical medicine (part 1). Medicine 65: 1-33, 1986. ; and
- [24044] Wang, C.-Y.; Huang, Y.-Q.; Shi, J.-O.; Marron, M. P.; Ruan, Q.-G.; Hawkins-Lee, B.; Ochoa, B.; She, J.-X. : Genetic homogeneity, high-resolution mapping, and mutation analysis of the u.
- [24045] Further studies establishing the function and utilities of GOT1 are found in John Hopkins OMIM database record ID 138180, and in cited publications numbered 11913-11914, 2988, 11915-11917, 11921, 11927-11929, 1882, 378 and 11930-11934 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Stress 70 Protein Chaperone, Microsome-associated, 60kDa (STCH, Accession NM\_006948) is another VGAM550 host target gene. STCH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STCH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STCH BINDING SITE, designated SEQ ID:13836, to the nu-

cleotide sequence of VGAM550 RNA, herein designated VGAM RNA, also designated SEQ ID:3261.

[24046] Another function of VGAM550 is therefore inhibition of Stress 70 Protein Chaperone, Microsome-associated, 60kDa (STCH, Accession NM\_006948), a gene which has peptide-independent atpase activity. Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STCH. The function of STCH has been established by previous studies. The stress-70 chaperone family consists of proteins that bind to denatured or incorrectly folded polypeptides and play a major role in the processing of cytosolic and secretory proteins. Otterson et al. (1994) cloned a human cDNA encoding a predicted 471-amino acid protein (60 kD) which they designated STCH. Brodsky et al. (1995) stated that the protein sequence is very similar to that of HSP70 (OMIM Ref. No. 140550) and BiP (OMIM Ref. No. 138120). As with other members of the family, the STCH protein contains an ATPase domain at the amino terminus whose activity was shown to be independent of peptide stimulation. The protein was found to be microsome-associated and constitutively expressed in all cell types examined. Brodsky et al. (1995) mapped the

STCH gene to chromosome 21q11.1 with a high-resolution somatic cell hybrid panel for chromosome 21 and by fluorescence in situ hybridization with a YAC containing the gene. By interspecific backcross analysis, Reeves et al. (1998) mapped the mouse Stch gene to chromosome 16.

[24047] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24048] Brodsky, G.; Otterson, G. A.; Parry, B. B.; Hart, I.; Patterson, D.; Kaye, F. J. : Localization of STCH to human chromosome 21q11.1. Genomics 30: 627–628, 1995. ; and

[24049] Otterson, G. A.; Flynn, G. C.; Kratzke, R. A.; Coxon, A.; Johnston, P. G.; Kaye, F. J. : Stch encodes the 'ATPase core' of a microsomal stress70 protein. EMBO J. 13: 1216–1225, 1994.

[24050] Further studies establishing the function and utilities of STCH are found in John Hopkins OMIM database record ID 601100, and in cited publications numbered 9629–9631 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 9 Open Reading Frame 14 (C9orf14, Accession XM\_098859) is another VGAM550 host target gene. C9orf14 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by C9orf14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C9orf14 BINDING SITE, designated SEQ ID:41911, to the nucleotide sequence of VGAM550 RNA, herein designated VGAM RNA, also designated SEQ ID:3261.

[24051] Another function of VGAM550 is therefore inhibition of Chromosome 9 Open Reading Frame 14 (C9orf14, Accession XM\_098859). Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C9orf14. DKFZp547A023 (Accession XM\_052065) is another VGAM550 host target gene. DKFZp547A023 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZp547A023, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547A023 BINDING SITE, designated SEQ ID:35944, to the nucleotide sequence of VGAM550 RNA, herein designated VGAM RNA, also designated SEQ ID:3261.



[24052] Another function of VGAM550 is therefore inhibition of DKFZp547A023 (Accession XM\_052065). Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547A023. 5-hydroxytryptamine (serotonin) Receptor 3A (HTR3A, Accession NM\_000869) is another VGAM550 host target gene. HTR3A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HTR3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HTR3A BINDING SITE, designated SEQ ID:6537, to the nucleotide sequence of VGAM550 RNA, herein designated VGAM RNA, also designated SEQ ID:3261.

[24053] Another function of VGAM550 is therefore inhibition of 5-hydroxytryptamine (serotonin) Receptor 3A (HTR3A, Accession NM\_000869). Accordingly, utilities of VGAM550 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTR3A. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 551

(VGAM551) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24054] VGAM551 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM551 was detected is described hereinabove with reference to Figs. 1–8.

[24055] VGAM551 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Leishmania RNA Virus 2–1. VGAM551 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24056] VGAM551 gene encodes a VGAM551 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM551 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM551 precursor RNA is designated SEQ ID:537, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:537 is located at position 3584 relative to the genome of Leishmania RNA Virus 2–1.

[24057] VGAM551 precursor RNA folds onto itself, forming

VGAM551 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24058] An enzyme complex designated DICER COMPLEX, `dices` the VGAM551 folded precursor RNA into VGAM551 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM551 RNA is designated SEQ ID:3262, and is provided hereinbelow with reference to the sequence listing part.

[24059] VGAM551 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM551 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM551 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24060] VGAM551 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM551 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM551 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM551 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM551 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24061] The complementary binding of VGAM551 RNA, herein designated VGAM RNA, to host target binding sites on VGAM551 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM551 host target RNA into VGAM551 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24062] It is appreciated that VGAM551 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM551 host target genes. The mRNA of each one of this plurality of VGAM551 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM551 RNA, herein designated VGAM RNA, and which when bound by VGAM551 RNA causes inhibition of translation of respective one or more VGAM551 host target proteins.

[24063] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM551 gene, herein designated VGAM GENE, on one or more VGAM551 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24064] It is yet further appreciated that a function of VGAM551 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of viral infection by Leishmania RNA Virus 2-1. Specific functions, and accordingly utilities, of VGAM551 correlate with, and may be deduced from, the identity of the host target genes which VGAM551 binds and inhibits,

and the function of these host target genes, as elaborated hereinbelow.

[24065] Nucleotide sequences of the VGAM551 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM551 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM551 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM551 are further described hereinbelow with reference to Table 1.

[24066] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM551 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM551 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24067] As mentioned hereinabove with reference to Fig. 1, a function of VGAM551 gene, herein designated VGAM is inhibition of expression of VGAM551 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM551 correlate with, and may be deduced from, the identity of the target genes which VGAM551 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[24068] Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 4 (SLC4A4, Accession NM\_003759) is a VGAM551 host target gene. SLC4A4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC4A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC4A4 BINDING SITE, designated SEQ ID:9840, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24069] A function of VGAM551 is therefore inhibition of Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 4 (SLC4A4, Accession NM\_003759), a gene which is a sodium bicarbonate cotransporter. Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC4A4. The function of SLC4A4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM222. Chromosome 20 Open Reading Frame 13 (C20orf13, Accession NM\_017714) is another



VGAM551 host target gene. C20orf13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf13 BINDING SITE, designated SEQ ID:19300, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24070] Another function of VGAM551 is therefore inhibition of Chromosome 20 Open Reading Frame 13 (C20orf13, Accession NM\_017714). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf13. DnaJ (Hsp40) Homolog, Subfamily C, Member 5 (DNAJC5, Accession XM\_028966) is another VGAM551 host target gene. DNAJC5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DNAJC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNAJC5 BINDING SITE, designated SEQ ID:30813, to the nucleotide sequence of VGAM551 RNA,

herein designated VGAM RNA, also designated SEQ ID:3262.

[24071] Another function of VGAM551 is therefore inhibition of DnaJ (Hsp40) Homolog, Subfamily C, Member 5 (DNAJC5, Accession XM\_028966). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNAJC5. FLJ10737 (Accession NM\_018198) is another VGAM551 host target gene. FLJ10737 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10737, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10737 BINDING SITE, designated SEQ ID:20067, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24072] Another function of VGAM551 is therefore inhibition of FLJ10737 (Accession NM\_018198). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10737. FLJ20079 (Accession NM\_017656) is another VGAM551 host target gene. FLJ20079 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ20079, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20079 BINDING SITE, designated SEQ ID:19167, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24073] Another function of VGAM551 is therefore inhibition of FLJ20079 (Accession NM\_017656). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20079. FLJ32499 (Accession NM\_144607) is another VGAM551 host target gene. FLJ32499 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ32499, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32499 BINDING SITE, designated SEQ ID:29422, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24074] Another function of VGAM551 is therefore inhibition of

FLJ32499 (Accession NM\_144607). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32499. Gamma-aminobutyric Acid (GABA) B Receptor, 1 (GABBR1, Accession NM\_021903) is another VGAM551 host target gene. GABBR1 BINDING SITE1 and GABBR1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GABBR1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GABBR1 BINDING SITE1 and GABBR1 BINDING SITE2, designated SEQ ID:22426 and SEQ ID:7208 respectively, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24075] Another function of VGAM551 is therefore inhibition of Gamma-aminobutyric Acid (GABA) B Receptor, 1 (GABBR1, Accession NM\_021903). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GABBR1. Nuclear Receptor Subfamily 4, Group A, Member 3 (NR4A3, Accession NM\_006981) is another VGAM551 host target gene. NR4A3 BINDING SITE is HOST TARGET binding site found

in the 5' untranslated region of mRNA encoded by NR4A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR4A3 BINDING SITE, designated SEQ ID:13844, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24076] Another function of VGAM551 is therefore inhibition of Nuclear Receptor Subfamily 4, Group A, Member 3 (NR4A3, Accession NM\_006981). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR4A3. SH3 Domain Binding Glutamic Acid-rich Protein Like 2 (SH3BGRL2, Accession NM\_031469) is another VGAM551 host target gene. SH3BGRL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SH3BGRL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SH3BGRL2 BINDING SITE, designated SEQ ID:25528, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA,

also designated SEQ ID:3262.

[24077] Another function of VGAM551 is therefore inhibition of SH3 Domain Binding Glutamic Acid-rich Protein Like 2 (SH3BGRL2, Accession NM\_031469). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SH3BGRL2. LOC128989 (Accession XM\_059310) is another VGAM551 host target gene. LOC128989 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC128989, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC128989 BINDING SITE, designated SEQ ID:36946, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24078] Another function of VGAM551 is therefore inhibition of LOC128989 (Accession XM\_059310). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC128989. LOC149276 (Accession XM\_097621) is another VGAM551 host target gene. LOC149276 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC149276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149276 BINDING SITE, designated SEQ ID:40975, to the nucleotide sequence of VGAM551 RNA, herein designated VGAM RNA, also designated SEQ ID:3262.

[24079] Another function of VGAM551 is therefore inhibition of LOC149276 (Accession XM\_097621). Accordingly, utilities of VGAM551 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149276. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 552 (VGAM552) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24080] VGAM552 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM552 was detected is described hereinabove with reference to Figs. 1–8.

[24081] VGAM552 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Human Adenovirus D. VGAM552 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24082] VGAM552 gene encodes a VGAM552 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM552 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM552 precursor RNA is designated SEQ ID:538, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:538 is located at position 980 relative to the genome of Human Adenovirus D.

[24083] VGAM552 precursor RNA folds onto itself, forming VGAM552 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.



[24084] An enzyme complex designated DICER COMPLEX, `dices` the VGAM552 folded precursor RNA into VGAM552 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM552 RNA is designated SEQ ID:3263, and is provided hereinbelow with reference to the sequence listing part.

[24085] VGAM552 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM552 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM552 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24086] VGAM552 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM552 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM552 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM552 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM552 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24087] The complementary binding of VGAM552 RNA, herein designated VGAM RNA, to host target binding sites on VGAM552 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM552 host tar-

get RNA into VGAM552 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24088] It is appreciated that VGAM552 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM552 host target genes. The mRNA of each one of this plurality of VGAM552 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM552 RNA, herein designated VGAM RNA, and which when bound by VGAM552 RNA causes inhibition of translation of respective one or more VGAM552 host target proteins.

[24089] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM552 gene, herein designated VGAM GENE, on one or more VGAM552 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24090] It is yet further appreciated that a function of VGAM552 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of viral infection by Human Adenovirus D. Specific functions, and accordingly utilities, of VGAM552 correlate with, and may be deduced from, the identity of the host target genes which VGAM552 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24091] Nucleotide sequences of the VGAM552 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM552 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM552 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM552 are further

described hereinbelow with reference to Table 1.

[24092] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM552 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM552 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24093] As mentioned hereinabove with reference to Fig. 1, a function of VGAM552 gene, herein designated VGAM is inhibition of expression of VGAM552 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM552 correlate with, and may be deduced from, the identity of the target genes which VGAM552 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24094] Apoptotic Protease Activating Factor (APAF1, Accession NM\_001160) is a VGAM552 host target gene. APAF1 BINDING SITE1 and APAF1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by APAF1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the

nucleotide sequences of APAF1 BINDING SITE1 and APAF1 BINDING SITE2, designated SEQ ID:6829 and SEQ ID:14868 respectively, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24095] A function of VGAM552 is therefore inhibition of Apoptotic Protease Activating Factor (APAF1, Accession NM\_001160), a gene which functions in the mitochondrial apoptotic pathway that leads to caspase 9 dependent activation of caspase 3. Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APAF1. The function of APAF1 has been established by previous studies.

Metastatic melanoma is a deadly cancer that fails to respond to conventional chemotherapy. Mutations in p53 (OMIM Ref. No. 191170) often occur in aggressive and chemoresistant cancers but are rarely observed in melanoma. Soengas et al. (2001) showed that metastatic melanomas often lose APAF1. Loss of APAF1 expression was accompanied by allelic loss in metastatic melanomas, but could be recovered in melanoma cell lines by treatment with the methylation inhibitor 5-aza-2-prime-deoxycytidine (5aza2dC). APAF1-negative

melanomas were invariably chemoresistant and were unable to execute a typical apoptotic program in response to p53 activation. Restoring physiologic levels of APAF1 through gene transfer or 5aza2dC treatment markedly enhanced chemosensitivity and rescued the apoptotic defects associated with APAF1 loss. Soengas et al. (2001) concluded that APAF1 is inactivated in metastatic melanomas, leading to defects in the execution of apoptotic cell death. Animal model experiments lend further support to the function of APAF1. Yoshida et al. (1998) also produced Apaf1-deficient mice which exhibited reduced apoptosis in the brain and striking craniofacial abnormalities with hyperproliferation of neuronal cells. Apaf1-deficient cells were resistant to a variety of apoptotic stimuli, and the processing of caspases-2, -3, and -8 was impaired. However, both Apaf1 -/- thymocytes and activated T lymphocytes were sensitive to Fas-induced killing, showing that Fas-mediated apoptosis in these cells is independent of Apaf1. These data indicated that Apaf1 plays a central role in the common events of mitochondria-dependent apoptosis in most death pathways and that this role is critical for normal development.

[24096] It is appreciated that the abovementioned animal model

for APAF1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[24097] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24098] Soengas, M. S.; Capodieci, P.; Polsky, D.; Mora, J.; Esteller, M.; Opitz-Araya, X.; McCombie, R.; Herman, J. G.; Gerald, W. L.; Lazebnik, Y. A.; Cordon-Cardo, C.; Lowe, S. W. : In-activation of the apoptosis effector Apaf-1 in malignant melanoma. Nature 409: 207-211, 2001. ; and

[24099] Yoshida, H.; Kong, Y.-Y.; Yoshida, R.; Elia, A. J.; Hakem, A.; Hakem, R.; Penninger, J. M.; Mak, T. W. : Apaf1 is required for mitochondrial pathways of apoptosis and brain development.

[24100] Further studies establishing the function and utilities of APAF1 are found in John Hopkins OMIM database record ID 602233, and in cited publications numbered 6292-6296, 230 and 5997-6000 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. High Mobility Group AT-hook 2 (HMGA2, Accession NM\_003483) is another VGAM552 host target gene. HMGA2 BINDING SITE is HOST TARGET



binding site found in the 5' untranslated region of mRNA encoded by HMGA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HMGA2 BINDING SITE, designated SEQ ID:9569, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24101] Another function of VGAM552 is therefore inhibition of High Mobility Group AT-hook 2 (HMGA2, Accession NM\_003483), a gene which may affect transcription and cell differentiation; shares common DNA-binding motif with other HMG HMG I/Y family members. Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HMGA2. The function of HMGA2 has been established by previous studies. Ashar et al. (1995) considered the HMGIC gene a good candidate for involvement in lipoma for several reasons, including the facts that it encodes a transcriptional regulating factor, that the pygmy mouse had disproportionately less fat than normal litter mates, and that the mouse gene maps to a region of chromosome 10 with homology of synteny to human

12q14–q15. Therefore, they cloned the human gene and investigated its possible role in lipomas. In FISH studies, Ashar et al. (1995) found apparent deletion of the 3–prime end of the HMGIC gene in translocations associated with lipoma. Chimeric transcripts were isolated from 2 lipomas in which HMGIC DNA–binding domains (AT hook motifs) were fused to either a LIM or an acidic trans–activator domain. The identification of a gene rearranged in a benign neoplastic process suggests a role for HMGIC in adipogenesis and mesenchymal differentiation. Animal model experiments lend further support to the function of HMGA2. To evaluate the role of the HMGIC component in the development of lipoma, Arlotta et al. (2000) expressed the 3 DNA–binding domains of HMGIC in transgenic mice. Despite the ubiquitous expression of the truncated HMGIC protein, the transgenic mice developed a selective abundance of fat tissue early in life, showed marked adipose tissue inflammation, and had an abnormally high incidence of lipomas. These findings demonstrated that the DNA–binding domain of HMGIC, in the absence of a C–terminal fusion partner, are sufficient to perturb adipogenesis and predispose to lipomas.

[24102] It is appreciated that the abovementioned animal model

for HMGA2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[24103] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24104] Ashar, H. R.; Schoenberg Fejzo, M.; Tkachenko, A.; Zhou, X.; Fletcher, J. A.; Weremowicz, S.; Morton, C. C.; Chada, K. : Disruption of the architectural factor HMGI-C: DNA-binding AT hook motifs fused in lipomas to distinct transcriptional regulatory domains. Cell 82: 57-65, 1995. ; and

[24105] Arlotta, P.; Tai, A. K.-F.; Manfioletti, G.; Clifford, C.; Jay, G.; Ono, S. J. : Transgenic mice expressing a truncated form of the high mobility group I-C protein develop adiposity and.

[24106] Further studies establishing the function and utilities of HMGA2 are found in John Hopkins OMIM database record ID 600698, and in cited publications numbered 10147-10159, 10242, 10397-10398, 347 and 10399 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Loss of Heterozygosity, 11, Chromosomal Region 2, Gene A (LOH11CR2A,

Accession NM\_014622) is another VGAM552 host target gene. LOH11CR2A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOH11CR2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOH11CR2A BINDING SITE, designated SEQ ID:15990, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24107] Another function of VGAM552 is therefore inhibition of Loss of Heterozygosity, 11, Chromosomal Region 2, Gene A (LOH11CR2A, Accession NM\_014622). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOH11CR2A. Protein Tyrosine Phosphatase, Receptor Type, J (PTPRJ, Accession NM\_002843) is another VGAM552 host target gene. PTPRJ BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PTPRJ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPRJ BINDING SITE,

designated SEQ ID:8732, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24108] Another function of VGAM552 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, J (PTPRJ, Accession NM\_002843), a gene which Receptor-type protein tyrosine phosphatase J. Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRJ. The function of PTPRJ has been established by previous studies. Experimental evidence indicates that specific protein tyrosine phosphatases (PTPases) interact with members of cascades to modulate biologic function differentiation and development. Experiments suggested that the PTPases PTP-beta (OMIM Ref. No. 176882) and PTP-epsilon (OMIM Ref. No. 600926) are involved in the early molecular events for in vitro differentiation of mouse erythroleukemia (MEL) as well as embryonic carcinoma (F9) cells (Watanabe et al., 1995).

[24109] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24110] Watanabe, T.; Mukouyama, Y.; Rhodes, M.; Thomas, M.;

Kume, T.; Oishi, M. : Chromosomal location of murine protein tyrosine phosphatase (Ptp<sup>rj</sup> and Ptp<sup>re</sup>) genes. *Genomics* 29: 793–795, 1995. ; and

[24111] Ruivenkamp, C. A. L.; van Wezel, T.; Zanon, C.; Stassen, A. P. M.; Vlcek, C.; Csikos, T.; Klous, A. M.; Tripodis, N.; Perakakis, A.; Boerrigter, L.; Groot, P. C.; Lindeman, J.; Mooi, W. J.

[24112] Further studies establishing the function and utilities of PTPRJ are found in John Hopkins OMIM database record ID 600925, and in cited publications numbered 10255–1025 and 1583 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ribosomal Protein S6 Kinase, 90kDa, Polypeptide 2 (RPS6KA2, Accession NM\_021135) is another VGAM552 host target gene. RPS6KA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RPS6KA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RPS6KA2 BINDING SITE, designated SEQ ID:22106, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24113] Another function of VGAM552 is therefore inhibition of Ribosomal Protein S6 Kinase, 90kDa, Polypeptide 2 (RPS6KA2, Accession NM\_021135), a gene which phosphorylates a wide range of substrates including ribosomal protein s6. Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RPS6KA2. The function of RPS6KA2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM216. Syndecan 4 (amphiglycan, ryudocan) (SDC4, Accession NM\_002999) is another VGAM552 host target gene. SDC4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDC4 BINDING SITE, designated SEQ ID:8892, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24114] Another function of VGAM552 is therefore inhibition of Syndecan 4 (amphiglycan, ryudocan) (SDC4, Accession NM\_002999), a gene which is a cell surface proteoglycan.

Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDC4. The function of SDC4 has been established by previous studies. The syndecans are trans-membrane heparan sulfate proteoglycans that appear to act as receptors or coreceptors involved in intracellular communication. Syndecan-4 was isolated from rat endothelial cells, as ryudocan, by Kojima et al. (1992) and from human epithelial and fibroblastic cells, under the designation amphiglycan, by David et al. (1992). By analysis of interspecific backcrosses, Spring et al. (1994) mapped the *Synd4* gene to distal mouse chromosome 2, very close to the *Ada* gene. Kojima et al. (1993) mapped the *SYND4* in the human to 20q12-q13 as would be predicted from the mouse location within no more than 2.2 cM of *Ada*. The *BMYC* gene is probably located on human chromosome 20 and has been shown to be located on mouse chromosome 2 (Ingvarsson et al., 1988; Asker et al., 1989). Although *BMYC* is a nonfunctional *MYC*-related gene, its location on chromosome 2 and chromosome 20 in the mouse and the human, respectively, extends the observation of Spring et al. (1994) that 4 members of the *MYC* gene family and 4 members of the syndecan gene



family are closely situated on 4 different chromosomes.

Yu et al. (1995) cloned the human ryudocan promoter.

Analysis of the sequence revealed the presence of several potential sites for nuclear transcription factor binding.

[24115] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24116] Spring, J.; Goldberger, O. A.; Jenkins, N. A.; Gilbert, D. J.; Copeland, N. G.; Bernfield, M. : Mapping of the syndecan genes in the mouse: linkage with members of the Myc gene family. Genomics 21: 597–601, 1994. ; and

[24117] Yu, H.; Humphries, D. E.; Watkins, M.; Karlinsky, J. B. : Molecular cloning of the human ryudocan promoter. Biochem. Biophys. Res. Commun. 212: 1139–1144, 1995.

[24118] Further studies establishing the function and utilities of SDC4 are found in John Hopkins OMIM database record ID 600017, and in cited publications numbered 8784, 11614–878 and 11616 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZp762E1312 (Accession NM\_018410) is another VGAM552 host target gene. DKFZp762E1312 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZp762E1312,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762E1312 BINDING SITE, designated SEQ ID:20453, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24119] Another function of VGAM552 is therefore inhibition of DKFZp762E1312 (Accession NM\_018410). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp762E1312. FLJ14082 (Accession NM\_025024) is another VGAM552 host target gene. FLJ14082 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14082, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14082 BINDING SITE, designated SEQ ID:24613, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24120] Another function of VGAM552 is therefore inhibition of FLJ14082 (Accession NM\_025024). Accordingly, utilities of

VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14082. FLJ20297 (Accession NM\_017951) is another VGAM552 host target gene. FLJ20297 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ20297, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20297 BINDING SITE, designated SEQ ID:19652, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24121] Another function of VGAM552 is therefore inhibition of FLJ20297 (Accession NM\_017951). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20297. FLJ20366 (Accession NM\_017786) is another VGAM552 host target gene. FLJ20366 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20366, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20366 BINDING SITE,

designated SEQ ID:19419, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24122] Another function of VGAM552 is therefore inhibition of FLJ20366 (Accession NM\_017786). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20366. KIAA0014 (Accession NM\_014665) is another VGAM552 host target gene. KIAA0014 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0014 BINDING SITE, designated SEQ ID:16119, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24123] Another function of VGAM552 is therefore inhibition of KIAA0014 (Accession NM\_014665). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0014. KIAA1274 (Accession XM\_166125) is another VGAM552 host target gene. KIAA1274 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1274, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1274 BINDING SITE, designated SEQ ID:43914, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24124] Another function of VGAM552 is therefore inhibition of KIAA1274 (Accession XM\_166125). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1274. P450RAI-2 (Accession NM\_019885) is another VGAM552 host target gene. P450RAI-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P450RAI-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P450RAI-2 BINDING SITE, designated SEQ ID:21270, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24125] Another function of VGAM552 is therefore inhibition of

P450RAI-2 (Accession NM\_019885). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P450RAI-2. SBBI26 (Accession NM\_018846) is another VGAM552 host target gene. SBBI26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SBBI26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SBBI26 BINDING SITE, designated SEQ ID:20832, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24126] Another function of VGAM552 is therefore inhibition of SBBI26 (Accession NM\_018846). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SBBI26. Serologically Defined Colon Cancer Antigen 3 (SDCCAG3, Accession NM\_006643) is another VGAM552 host target gene. SDCCAG3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDCCAG3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDCCAG3 BINDING SITE, designated SEQ ID:13436, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24127] Another function of VGAM552 is therefore inhibition of Serologically Defined Colon Cancer Antigen 3 (SDCCAG3, Accession NM\_006643). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDCCAG3. Syntaxin 1B2 (STX1B2, Accession NM\_052874) is another VGAM552 host target gene. STX1B2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STX1B2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STX1B2 BINDING SITE, designated SEQ ID:27456, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24128] Another function of VGAM552 is therefore inhibition of Syntaxin 1B2 (STX1B2, Accession NM\_052874). Accordingly, utilities of VGAM552 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with STX1B2. LOC120839 (Accession XM\_071729) is another VGAM552 host target gene. LOC120839 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC120839, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120839 BINDING SITE, designated SEQ ID:37415, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24129] Another function of VGAM552 is therefore inhibition of LOC120839 (Accession XM\_071729). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120839. LOC150245 (Accession XM\_097843) is another VGAM552 host target gene. LOC150245 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150245, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150245 BINDING SITE, designated SEQ ID:41163, to



the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24130] Another function of VGAM552 is therefore inhibition of LOC150245 (Accession XM\_097843). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150245. LOC150776 (Accession XM\_032542) is another VGAM552 host target gene. LOC150776 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150776, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150776 BINDING SITE, designated SEQ ID:31678, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24131] Another function of VGAM552 is therefore inhibition of LOC150776 (Accession XM\_032542). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150776. LOC151610 (Accession XM\_087245) is another VGAM552 host target gene. LOC151610 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC151610, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151610 BINDING SITE, designated SEQ ID:39137, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24132] Another function of VGAM552 is therefore inhibition of LOC151610 (Accession XM\_087245). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151610. LOC199848 (Accession XM\_117144) is another VGAM552 host target gene. LOC199848 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC199848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199848 BINDING SITE, designated SEQ ID:43251, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24133] Another function of VGAM552 is therefore inhibition of LOC199848 (Accession XM\_117144). Accordingly, utilities

of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199848. LOC220045 (Accession XM\_167820) is another VGAM552 host target gene. LOC220045 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220045, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220045 BINDING SITE, designated SEQ ID:44862, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24134] Another function of VGAM552 is therefore inhibition of LOC220045 (Accession XM\_167820). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220045. LOC91097 (Accession XM\_035977) is another VGAM552 host target gene. LOC91097 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91097, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC91097 BINDING SITE, designated SEQ ID:32370, to the nucleotide sequence of VGAM552 RNA, herein designated VGAM RNA, also designated SEQ ID:3263.

[24135] Another function of VGAM552 is therefore inhibition of LOC91097 (Accession XM\_035977). Accordingly, utilities of VGAM552 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91097. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 553 (VGAM553) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24136] VGAM553 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM553 was detected is described hereinabove with reference to Figs. 1–8.

[24137] VGAM553 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Parainfluenza Virus 3. VGAM553 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24138] VGAM553 gene encodes a VGAM553 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM553 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM553 precursor RNA is designated SEQ ID:539, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:539 is located at position 7376 relative to the genome of Bovine Parainfluenza Virus 3.

[24139] VGAM553 precursor RNA folds onto itself, forming VGAM553 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24140] An enzyme complex designated DICER COMPLEX, `dices` the VGAM553 folded precursor RNA into VGAM553 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM553 RNA is designated SEQ ID:3264, and is provided hereinbelow with reference to the sequence listing part.

[24141] VGAM553 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM553 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM553 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24142] VGAM553 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM553 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM553 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM553 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM553 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24143] The complementary binding of VGAM553 RNA, herein designated VGAM RNA, to host target binding sites on VGAM553 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM553 host target RNA into VGAM553 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24144] It is appreciated that VGAM553 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM553 host target genes. The mRNA of each one of this plurality of VGAM553 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM553 RNA, herein designated VGAM RNA, and which when bound by VGAM553 RNA causes inhibition of translation of respective one or more VGAM553 host target proteins.

[24145] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM553 gene, herein designated VGAM GENE, on one or more VGAM553 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these



other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[24146] It is yet further appreciated that a function of VGAM553 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM553 include diagnosis, prevention and treatment of viral infection by Bovine Parainfluenza Virus 3. Specific functions, and accordingly utilities, of VGAM553 correlate with, and may be deduced from, the identity of the host target genes which VGAM553 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24147] Nucleotide sequences of the VGAM553 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM553 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM553 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM553 are further described hereinbelow with reference to Table 1.

[24148] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM553 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM553 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24149] As mentioned hereinabove with reference to Fig. 1, a function of VGAM553 gene, herein designated VGAM is inhibition of expression of VGAM553 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM553 correlate with, and may be deduced from, the identity of the target genes which VGAM553 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24150] NDRG Family Member 3 (NDRG3, Accession NM\_022477) is a VGAM553 host target gene. NDRG3 BINDING SITE1 and NDRG3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by NDRG3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDRG3 BINDING SITE1 and NDRG3 BINDING SITE2, designated SEQ ID:22848 and SEQ ID:25724 respectively, to the nucleotide sequence of VGAM553 RNA, herein designated VGAM RNA, also designated SEQ

ID:3264.

[24151] A function of VGAM553 is therefore inhibition of NDRG Family Member 3 (NDRG3, Accession NM\_022477). Accordingly, utilities of VGAM553 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDRG3. LOC115073 (Accession XM\_055193) is another VGAM553 host target gene. LOC115073 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115073, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115073 BINDING SITE, designated SEQ ID:36234, to the nucleotide sequence of VGAM553 RNA, herein designated VGAM RNA, also designated SEQ ID:3264.

[24152] Another function of VGAM553 is therefore inhibition of LOC115073 (Accession XM\_055193). Accordingly, utilities of VGAM553 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115073. LOC147072 (Accession XM\_017121) is another VGAM553 host target gene. LOC147072 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147072, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147072 BINDING SITE, designated SEQ ID:30299, to the nucleotide sequence of VGAM553 RNA, herein designated VGAM RNA, also designated SEQ ID:3264.

[24153] Another function of VGAM553 is therefore inhibition of LOC147072 (Accession XM\_017121). Accordingly, utilities of VGAM553 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147072. LOC148085 (Accession XM\_097388) is another VGAM553 host target gene. LOC148085 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148085, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148085 BINDING SITE, designated SEQ ID:40867, to the nucleotide sequence of VGAM553 RNA, herein designated VGAM RNA, also designated SEQ ID:3264.

[24154] Another function of VGAM553 is therefore inhibition of LOC148085 (Accession XM\_097388). Accordingly, utilities of VGAM553 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC148085. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 554 (VGAM554) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24155] VGAM554 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM554 was detected is described hereinabove with reference to Figs. 1–8.

[24156] VGAM554 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Spodoptera Exigua Nucleopolyhedrovirus. VGAM554 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24157] VGAM554 gene encodes a VGAM554 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM554 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM554 precursor RNA is designated SEQ

ID:540, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:540 is located at position 47344 relative to the genome of Spodoptera Exigua Nucleopolyhedrovirus.

[24158] VGAM554 precursor RNA folds onto itself, forming VGAM554 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24159] An enzyme complex designated DICER COMPLEX, `dices` the VGAM554 folded precursor RNA into VGAM554 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 55%) nucleotide sequence of VGAM554 RNA is designated SEQ ID:3265, and is provided hereinbelow with reference to the sequence

listing part.

[24160] VGAM554 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM554 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM554 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24161] VGAM554 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM554 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM554 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM554 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM554 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24162] The complementary binding of VGAM554 RNA, herein designated VGAM RNA, to host target binding sites on VGAM554 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM554 host target RNA into VGAM554 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24163] It is appreciated that VGAM554 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM554 host target genes. The mRNA of each one of this plurality of VGAM554 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM554 RNA, herein designated VGAM



RNA, and which when bound by VGAM554 RNA causes inhibition of translation of respective one or more VGAM554 host target proteins.

[24164] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM554 gene, herein designated VGAM GENE, on one or more VGAM554 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24165] It is yet further appreciated that a function of VGAM554 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM554 include diagnosis, prevention and treatment of viral infection by Spodoptera Exigua Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM554 correlate with, and may be deduced from, the identity of the host target genes which VGAM554 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24166] Nucleotide sequences of the VGAM554 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM554 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM554 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM554 are further described hereinbelow with reference to Table 1.

[24167] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM554 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM554 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24168] As mentioned hereinabove with reference to Fig. 1, a function of VGAM554 gene, herein designated VGAM is

inhibition of expression of VGAM554 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM554 correlate with, and may be deduced from, the identity of the target genes which VGAM554 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24169] EphA8 (EPA8, Accession NM\_020526) is a VGAM554 host target gene. EPA8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPA8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPA8 BINDING SITE, designated SEQ ID:21743, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24170] A function of VGAM554 is therefore inhibition of EphA8 (EPA8, Accession NM\_020526), a gene which Eph-related receptor tyrosine kinase A8. Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPA8. The function of EPA8 and its association with various diseases and clinical conditions, has been established by

previous studies, as described hereinabove with reference to VGAM494. Hormonally Upregulated Neu-associated Kinase (HUNK, Accession NM\_014586) is another VGAM554 host target gene. HUNK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HUNK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HUNK BINDING SITE, designated SEQ ID:15945, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24171] Another function of VGAM554 is therefore inhibition of Hormonally Upregulated Neu-associated Kinase (HUNK, Accession NM\_014586). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUNK. Integrin, Alpha 11 (ITGA11, Accession NM\_012211) is another VGAM554 host target gene. ITGA11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGA11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of ITGA11 BINDING SITE, designated SEQ ID:14512, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24172] Another function of VGAM554 is therefore inhibition of Integrin, Alpha 11 (ITGA11, Accession NM\_012211), a gene which acts as a collagen I receptor. Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGA11. The function of ITGA11 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM206. Nucleolar Protein 3 (apoptosis repressor with CARD domain) (NOL3, Accession NM\_003946) is another VGAM554 host target gene. NOL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NOL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NOL3 BINDING SITE, designated SEQ ID:10064, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24173] Another function of VGAM554 is therefore inhibition of Nucleolar Protein 3 (apoptosis repressor with CARD domain) (NOL3, Accession NM\_003946), a gene which inhibits CASP2 and CASP8 and interacts with splicing factors. Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NOL3. The function of NOL3 has been established by previous studies. By searching an EST database for apoptosis-regulating proteins with homology to the caspase recruitment domain (CARD) of caspase-9 (CASP9; 602234), Koseki et al. (1998) identified a cDNA encoding ARC (apoptosis repressor with CARD). Sequence analysis predicted that the 208-amino acid ARC protein contains an N-terminal CARD and a C-terminal region rich in proline and glutamic acid. Northern blot analysis detected 5.5- and 1.0-kb ARC transcripts in skeletal muscle and heart, but no expression was detected in brain, placenta, lung, liver, kidney, pancreas, and lymphoid/hematopoietic tissues. To identify proteins involved in RNA processing, Stoss et al. (1999) used a yeast 2-hybrid screen with SRp30c (SFRS9; 601943) as bait on a HeLa library. They isolated a cDNA encoding a protein that they designated NOP30 (nucleolar protein of 30 kD) based on

SDS–PAGE analysis. The authors also identified a cDNA encoding a smaller isoform that they termed MYC (muscle–enriched cytosolic protein), which is created by a frameshift and is identical to the ARC protein reported by Koseki et al. (1998). MYC did not interact with SFRS9. Sequence analysis of the 219–amino acid NOP30 protein predicted that it contains a highly acidic N terminus and a basic C terminus enriched with arginines, serines, and prolines and having multiple phosphorylation sites. Northern blot analysis detected 1.8– and 1.3–kb NOP30 transcripts, with highest expression in heart and skeletal muscle and weak expression in other tissues. In contrast, SFRS9 is relatively strongly and ubiquitously expressed as a 1.35–kb transcript. In situ hybridization analysis showed that NOP30 is expressed in the pia mater, a tissue surrounding the brain containing blood vessels lined with smooth muscle cells. Binding analysis indicated that NOP30 binds to itself and that the N and C termini of NOP30 interact with SFRS9 through its RS domain. Confocal microscopy demonstrated that NOP30, through its arginine–rich C terminus, colocalizes with B23 (NPM1; 164040) in the granular component of nucleoli; however, the majority of NOP30 was localized in the fibrillar com–

ponent. NOP30 and SFRS9 colocalized in the nucleoplasm. In contrast, MYP, with its acidic N terminus, was predominantly localized in the cytoplasm.

[24174] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24175] Koseki, T.; Inohara, N.; Chen, S.; Nunez, G. : ARC, an inhibitor of apoptosis expressed in skeletal muscle and heart that interacts selectively with caspases. Proc. Nat. Acad. Sci. 95: 5156–5160, 1998. ; and

[24176] Stoss, O.; Schwaiger, F.–W.; Cooper, T. A.; Stamm, S. : Alternative splicing determines the intracellular localization of the novel nuclear protein Nop30 and its interaction with the sp.

[24177] Further studies establishing the function and utilities of NOL3 are found in John Hopkins OMIM database record ID 605235, and in cited publications numbered 7309–731 and 940 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RecQ Protein-like 5 (RECQL5, Accession NM\_004259) is another VGAM554 host target gene. RECQL5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RECQL5, corresponding to a HOST



TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RECQL5 BINDING SITE, designated SEQ ID:10447, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24178] Another function of VGAM554 is therefore inhibition of RecQ Protein-like 5 (RECQL5, Accession NM\_004259). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RECQL5. SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily D, Member 2 (SMARCD2, Accession NM\_003077) is another VGAM554 host target gene. SMARCD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SMARCD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMARCD2 BINDING SITE, designated SEQ ID:9050, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24179] Another function of VGAM554 is therefore inhibition of

SWI/SNF Related, Matrix Associated, Actin Dependent  
Regulator of Chromatin, Subfamily D, Member 2

(SMARCD2, Accession NM\_003077), a gene which is involved in chromatin remodeling. Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMARCD2. The function of SMARCD2 has been established by previous studies. Chromatin is actively remodeled during development. Chromatin remodeling of certain genes appears to precede their transcriptional activation. In yeast, the multisubunit SWI/SNF complex is thought to be responsible for chromatin remodeling. Wang et al. (1996) isolated an analogous SWI/SNF complex from the human YT cell line. They found that the resultant complexes are composed of 9 to 12 polypeptides, which they termed BAFs (for BRG1-associated factors). Wang et al. (1996) cloned the BAF60b subunit based on its homology with BAF60a (OMIM Ref. No. 601735). BAF60b encodes a polypeptide of 475 amino acids and is homologous to the yeast SWP73 gene, a component of the yeast SWI/SNF chromatin remodeling complex. The human genes BAF60a, BAF60b, and BAF60c (OMIM Ref. No. 601737) are highly homologous. By PCR of a somatic cell hybrid panel

and radiation hybrid analysis, Ring et al. (1998) mapped the SMARCD2 gene to chromosome 17q23–q24

[24180] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24181] Ring, H. Z.; Vameghi–Meyers, V.; Wang, W.; Crabtree, G. R.; Francke, U. : Five SWI/SNF–related, matrix–associated, actin–dependent regulator of chromatin (SMARC) genes are dispersed in the human genome. Genomics 51: 140–143, 1998. ; and

[24182] Wang, W.; Xue, Y.; Zhou, S.; Kuo, A.; Cairns, B. R.; Crabtree, G. R. : Diversity and specialization of mammalian SWI/SNF complexes. Genes Dev. 10: 2117–2130, 1996.

[24183] Further studies establishing the function and utilities of SMARCD2 are found in John Hopkins OMIM database record ID 601736, and in cited publications numbered 9322–9323 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transmembrane, Cochlear Expressed, 1 (TMC1, Accession NM\_138691) is another VGAM554 host target gene. TMC1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by TMC1, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMC1 BINDING SITE, designated SEQ ID:28933, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24184] Another function of VGAM554 is therefore inhibition of Transmembrane, Cochlear Expressed, 1 (TMC1, Accession NM\_138691), a gene which is required for normal function of cochlear hair cells. Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMC1. The function of TMC1 has been established by previous studies. By positional cloning, Kurima et al. (2002) identified the gene mutant in a form of autosomal dominant deafness (DFNA36; 606705) and of recessive deafness (DFNB7/B11; 600974) that map to the same interval on 9q13–q21. The authors evaluated several candidate genes in the critical region but found no mutations in the deaf families. To identify additional DFNA36/B7/B11 candidate genes based upon sequence similarity to related genes elsewhere in the genome, they initiated a systematic BLAST analysis of segments of genomic DNA sequence in the critical region. One sequence was found to be similar to a

predicted gene (subsequently named TMC2; 606707) on 20p13. They used conserved sequences between TMC2 and the query sequence (subsequently named TMC1) on chromosome 9q13–q21 to design primers for amplifying potential TMC1 transcripts from a human fetal brain cDNA library. Kurima et al. (2002) found the longest open reading frame to be 2,283 nucleotides, predicting an 87–kD protein. The TMC1 protein is predicted to contain 6 transmembrane domains and to have cytoplasmic orientation of N and C termini. Kurima et al. (2002) obtained the orthologous mouse *Tmc1* cDNA by RT–PCR and 5–prime and 3–prime RACE of mouse inner–ear cDNA. They found that in the mouse, *Tmc1* mRNA is expressed in hair cells of the postnatal cochlea and vestibular end organs and is required for normal function of cochlear hair cells. Animal model experiments lend further support to the function of TMC1. Vreugde et al. (2002) identified a missense mutation in the *Tmc1* gene in the mouse deaf mutant 'Beethoven' (Bth). Thus it is a mouse model for autosomal dominant progressive hearing loss (DFNA36; 606705). Similarly, the recessive deafness mutation *dn*, which maps to mouse chromosome 19, is a model of profound congenital deafness caused by mutations in the TMC1 gene:

DFNB7 (OMIM Ref. No. 600974), also known as DFNB11.

[24185] It is appreciated that the abovementioned animal model for TMC1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[24186] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24187] Kurima, K.; Peters. L. M.; Yang, Y.; Riazuddin, S.; Ahmed, Z. M.; Naz, S.; Arnaud, D.; Drury, S.; Mo, J.; Makishima, T.; Ghosh, M.; Menon, P. S. N.; and 13 others : Dominant and recessive deafness caused by mutations of a novel gene, TMC1, required for cochlear hair-cell function. *Nature Genet.* 30: 277–284, 2002. ; and

[24188] Vreugde, S.; Erven, A.; Kros, C. J.; Marcotti, W.; Fuches, H.; Kurima, K.; Wilcox, E. R.; Friedman, T. B.; Griffith, A. J.; Balling, R.; de Angelis, M. H.; Avraham, K. B.; Steel, K. P.

[24189] Further studies establishing the function and utilities of TMC1 are found in John Hopkins OMIM database record ID 606706, and in cited publications numbered 7799 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Bobby Sox Homolog (*Drosophila*) (BBX, Accession NM\_020235) is another

VGAM554 host target gene. BBX BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by BBX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BBX BINDING SITE, designated SEQ ID:21504, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24190] Another function of VGAM554 is therefore inhibition of Bobby Sox Homolog (Drosophila) (BBX, Accession NM\_020235). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BBX. EphA7 (EPHA7, Accession NM\_004440) is another VGAM554 host target gene. EPHA7 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by EPHA7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPHA7 BINDING SITE, designated SEQ ID:10724, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ

ID:3265.

[24191] Another function of VGAM554 is therefore inhibition of EphA7 (EPHA7, Accession NM\_004440). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPHA7. FLJ14213 (Accession NM\_024841) is another VGAM554 host target gene. FLJ14213 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14213, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14213 BINDING SITE, designated SEQ ID:24251, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24192] Another function of VGAM554 is therefore inhibition of FLJ14213 (Accession NM\_024841). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14213. FLJ20004 (Accession XM\_170889) is another VGAM554 host target gene. FLJ20004 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20004, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20004 BINDING SITE, designated SEQ ID:45646, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24193] Another function of VGAM554 is therefore inhibition of FLJ20004 (Accession XM\_170889). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20004. FLJ20378 (Accession NM\_017795) is another VGAM554 host target gene. FLJ20378 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20378, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20378 BINDING SITE, designated SEQ ID:19434, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24194] Another function of VGAM554 is therefore inhibition of FLJ20378 (Accession NM\_017795). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ20378. KIAA0711 (Accession NM\_014867) is another VGAM554 host target gene. KIAA0711 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA0711, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0711 BINDING SITE, designated SEQ ID:16961, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24195] Another function of VGAM554 is therefore inhibition of KIAA0711 (Accession NM\_014867). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0711. KIAA0992 (Accession NM\_016081) is another VGAM554 host target gene. KIAA0992 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0992, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0992 BINDING SITE, designated SEQ ID:18158, to the

nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24196] Another function of VGAM554 is therefore inhibition of KIAA0992 (Accession NM\_016081). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0992. KIAA1130 (Accession XM\_031104) is another VGAM554 host target gene. KIAA1130 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1130, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1130 BINDING SITE, designated SEQ ID:31280, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24197] Another function of VGAM554 is therefore inhibition of KIAA1130 (Accession XM\_031104). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1130. Leucine-rich Repeat Protein, Neuronal 3 (LRRN3, Accession XM\_045261) is another VGAM554 host target gene. LRRN3 BINDING SITE is HOST TARGET binding

site found in the 5` untranslated region of mRNA encoded by LRRN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRRN3 BINDING SITE, designated SEQ ID:34401, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24198] Another function of VGAM554 is therefore inhibition of Leucine-rich Repeat Protein, Neuronal 3 (LRRN3, Accession XM\_045261). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRRN3. MGC22014 (Accession XM\_035307) is another VGAM554 host target gene. MGC22014 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC22014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC22014 BINDING SITE, designated SEQ ID:32216, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24199] Another function of VGAM554 is therefore inhibition of MGC22014 (Accession XM\_035307). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC22014. MGC3248 (Accession NM\_032486) is another VGAM554 host target gene. MGC3248 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC3248, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC3248 BINDING SITE, designated SEQ ID:26236, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24200] Another function of VGAM554 is therefore inhibition of MGC3248 (Accession NM\_032486). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC3248. PDZ Domain Containing 2 (PDZD2, Accession XM\_087705) is another VGAM554 host target gene. PDZD2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PDZD2, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDZD2 BINDING SITE, designated SEQ ID:39388, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24201] Another function of VGAM554 is therefore inhibition of PDZ Domain Containing 2 (PDZD2, Accession XM\_087705). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDZD2. PRO2859 (Accession NM\_018543) is another VGAM554 host target gene. PRO2859 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO2859, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2859 BINDING SITE, designated SEQ ID:20615, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24202] Another function of VGAM554 is therefore inhibition of PRO2859 (Accession NM\_018543). Accordingly, utilities of

VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2859. Protein Serine Kinase H1 (PSKH1, Accession XM\_043047) is another VGAM554 host target gene. PSKH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSKH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSKH1 BINDING SITE, designated SEQ ID:33867, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24203] Another function of VGAM554 is therefore inhibition of Protein Serine Kinase H1 (PSKH1, Accession XM\_043047). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSKH1. LOC123242 (Accession XM\_063548) is another VGAM554 host target gene. LOC123242 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC123242, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of LOC123242 BINDING SITE, designated SEQ ID:37239, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24204] Another function of VGAM554 is therefore inhibition of LOC123242 (Accession XM\_063548). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC123242. LOC127703 (Accession XM\_059172) is another VGAM554 host target gene. LOC127703 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC127703, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127703 BINDING SITE, designated SEQ ID:36908, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24205] Another function of VGAM554 is therefore inhibition of LOC127703 (Accession XM\_059172). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127703. LOC157273 (Accession XM\_098743) is an-



other VGAM554 host target gene. LOC157273 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157273 BINDING SITE, designated SEQ ID:41781, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24206] Another function of VGAM554 is therefore inhibition of LOC157273 (Accession XM\_098743). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157273. LOC221463 (Accession XM\_166374) is another VGAM554 host target gene. LOC221463 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221463, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221463 BINDING SITE, designated SEQ ID:44204, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24207] Another function of VGAM554 is therefore inhibition of LOC221463 (Accession XM\_166374). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221463. LOC253001 (Accession XM\_171711) is another VGAM554 host target gene. LOC253001 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253001, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253001 BINDING SITE, designated SEQ ID:46056, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24208] Another function of VGAM554 is therefore inhibition of LOC253001 (Accession XM\_171711). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253001. LOC56965 (Accession NM\_020213) is another VGAM554 host target gene. LOC56965 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC56965, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC56965 BINDING SITE, designated SEQ ID:21453, to the nucleotide sequence of VGAM554 RNA, herein designated VGAM RNA, also designated SEQ ID:3265.

[24209] Another function of VGAM554 is therefore inhibition of LOC56965 (Accession NM\_020213). Accordingly, utilities of VGAM554 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC56965. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 555 (VGAM555) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24210] VGAM555 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM555 was detected is described hereinabove with reference to Figs. 1–8.

[24211] VGAM555 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Spodoptera Exigua Nucleopolyhedrovirus. VGAM555 host target gene, herein

designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24212] VGAM555 gene encodes a VGAM555 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM555 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM555 precursor RNA is designated SEQ ID:541, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:541 is located at position 47117 relative to the genome of Spodoptera Exigua Nucleopolyhedrovirus.

[24213] VGAM555 precursor RNA folds onto itself, forming VGAM555 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24214] An enzyme complex designated DICER COMPLEX, `dices` the VGAM555 folded precursor RNA into VGAM555 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM555 RNA is designated SEQ ID:3266, and is provided hereinbelow with reference to the sequence listing part.

[24215] VGAM555 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM555 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM555 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24216] VGAM555 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM555 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM555 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM555 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM555 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24217] The complementary binding of VGAM555 RNA, herein designated VGAM RNA, to host target binding sites on VGAM555 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM555 host target RNA into VGAM555 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[24218] It is appreciated that VGAM555 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM555 host target genes. The mRNA of each one of this plurality of VGAM555 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM555 RNA, herein designated VGAM RNA, and which when bound by VGAM555 RNA causes inhibition of translation of respective one or more VGAM555 host target proteins.

[24219] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM555 gene, herein designated VGAM GENE, on one or more VGAM555 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24220] It is yet further appreciated that a function of VGAM555 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM555 include diagnosis, prevention and treatment of viral infection by Spodoptera Exigua Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM555 correlate with, and may be deduced from, the identity of the host target genes which VGAM555 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24221] Nucleotide sequences of the VGAM555 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM555 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM555 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM555 are further described hereinbelow with reference to Table 1.

[24222] Nucleotide sequences of host target binding sites, such as



BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM555 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM555 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24223] As mentioned hereinabove with reference to Fig. 1, a function of VGAM555 gene, herein designated VGAM is inhibition of expression of VGAM555 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM555 correlate with, and may be deduced from, the identity of the target genes which VGAM555 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24224] Protein Tyrosine Kinase 2 Beta (PTK2B, Accession NM\_004103) is a VGAM555 host target gene. PTK2B BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PTK2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTK2B BINDING SITE, designated SEQ ID:10312, to the nucleotide sequence of VGAM555 RNA, herein designated

VGAM RNA, also designated SEQ ID:3266.

[24225] A function of VGAM555 is therefore inhibition of Protein Tyrosine Kinase 2 Beta (PTK2B, Accession NM\_004103), a gene which is involved in calcium induced regulation of ion channel and activation of the map kinase signaling pathway. Accordingly, utilities of VGAM555 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTK2B. The function of PTK2B has been established by previous studies. Lev et al. (1995) showed that the PYK2 protein undergoes rapid tyrosine phosphorylation in response to various stimuli that elevate intracellular calcium concentration, such as addition of bradykinin, a neuropeptide hormone that binds to a G protein-coupled receptor and in turn stimulates phosphatidylinositol hydrolysis. PYK2 is also tyrosine phosphorylated following activation of the nicotinic acetylcholine receptor (see OMIM Ref. No. 100690), by membrane depolarization, and by treatment of cells with a calcium ionophore. Protein kinase C (OMIM Ref. No. 176960) activation also induces PYK2 phosphorylation. Activation of PYK2 leads to the modulation of ion channel function and activation of the MAP kinase signaling pathway. Lev et al. (1995) proposed that PYK2 may represent an important

signaling intermediate between neuropeptide activated receptors or neurotransmitters that increase calcium flux and the downstream signals that regulate neuronal activity. PYK2 may also provide a mechanism for a variety of short- and long-term calcium-dependent signaling events in the nervous system. Hepatitis B virus (HBV) causes acute and chronic infection of the liver and is also a risk factor for hepatic cancer. The virus has only 4 open reading frames, 3 of which encode the capsid, envelope, and polymerase proteins. The fourth encodes HBX, a poorly expressed protein required for viral replication (Ganem, 2001). Bouchard et al. (2001) showed that HBX induces release of calcium into the cytoplasm, presumably from mitochondria or endoplasmic reticulum. HBX expression thereby induces activation of PYK2, which activates SRC (OMIM Ref. No. 190090) and HBV DNA replication. Inhibition of PYK2 or calcium signaling mediated by mitochondrial calcium channels could block HBV DNA replication, and enhancement of cytoplasmic calcium was able to substitute for HBX in stimulating HBV DNA replication.

[24226] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24227] Lev, S.; Moreno, H.; Martinez, R.; Canoll, P.; Peles, E.; Musacchio, J. M.; Plowman, G. D.; Rudy, B.; Schlessinger, J. : Protein tyrosine kinase PYK2 involved in  $\text{Ca}^{2+}$ -induced regulation of ion channel and MAP kinase functions. *Nature* 376: 737–745, 1995. ; and

[24228] Bouchard, M. J.; Wang, L.-H.; Schneider, R. J. : Calcium signaling by HBx protein in hepatitis B virus DNA replication. *Science* 294: 2376–2378, 2001.

[24229] Further studies establishing the function and utilities of PTK2B are found in John Hopkins OMIM database record ID 601212, and in cited publications numbered 6887–6893 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ10583 (Accession NM\_018148) is another VGAM555 host target gene. FLJ10583 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10583, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10583 BINDING SITE, designated SEQ ID:19949, to the nucleotide sequence of VGAM555 RNA, herein designated VGAM RNA, also designated SEQ ID:3266.

[24230] Another function of VGAM555 is therefore inhibition of FLJ10583 (Accession NM\_018148). Accordingly, utilities of VGAM555 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10583. MGC4562 (Accession NM\_133375) is another VGAM555 host target gene. MGC4562 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC4562, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4562 BINDING SITE, designated SEQ ID:28496, to the nucleotide sequence of VGAM555 RNA, herein designated VGAM RNA, also designated SEQ ID:3266.

[24231] Another function of VGAM555 is therefore inhibition of MGC4562 (Accession NM\_133375). Accordingly, utilities of VGAM555 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4562. Trimethyllysine Hydroxylase, Epsilon (TMLHE, Accession NM\_018196) is another VGAM555 host target gene. TMLHE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMLHE, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMLHE BINDING SITE, designated SEQ ID:20062, to the nucleotide sequence of VGAM555 RNA, herein designated VGAM RNA, also designated SEQ ID:3266.

[24232] Another function of VGAM555 is therefore inhibition of Trimethyllysine Hydroxylase, Epsilon (TMLHE, Accession NM\_018196). Accordingly, utilities of VGAM555 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMLHE. LOC139673 (Accession XM\_071645) is another VGAM555 host target gene. LOC139673 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC139673, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC139673 BINDING SITE, designated SEQ ID:37403, to the nucleotide sequence of VGAM555 RNA, herein designated VGAM RNA, also designated SEQ ID:3266.

[24233] Another function of VGAM555 is therefore inhibition of LOC139673 (Accession XM\_071645). Accordingly, utilities

of VGAM555 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC139673. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 556 (VGAM556) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24234] VGAM556 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM556 was detected is described hereinabove with reference to Figs. 1–8.

[24235] VGAM556 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Spodoptera Exigua Nucleopolyhedrovirus. VGAM556 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24236] VGAM556 gene encodes a VGAM556 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM556 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM556 precursor RNA is designated SEQ ID:542, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:542 is located at position 47004 relative to the genome of Spodoptera Exigua Nucleopolyhedrovirus.

[24237] VGAM556 precursor RNA folds onto itself, forming VGAM556 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24238] An enzyme complex designated DICER COMPLEX, `dices` the VGAM556 folded precursor RNA into VGAM556 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM556 RNA is designated SEQ ID:3267, and



is provided hereinbelow with reference to the sequence listing part.

[24239] VGAM556 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM556 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM556 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24240] VGAM556 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM556 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM556 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM556 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM556 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24241] The complementary binding of VGAM556 RNA, herein designated VGAM RNA, to host target binding sites on VGAM556 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM556 host target RNA into VGAM556 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24242] It is appreciated that VGAM556 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM556 host target genes. The mRNA of each one of this plurality of VGAM556 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM556 RNA, herein designated VGAM RNA, and which when bound by VGAM556 RNA causes inhibition of translation of respective one or more VGAM556 host target proteins.

[24243] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM556 gene, herein designated VGAM GENE, on one or more VGAM556 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24244] It is yet further appreciated that a function of VGAM556 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of viral infection by Spodoptera Exigua Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM556 correlate with, and may be deduced from, the identity of the host target genes which VGAM556 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24245] Nucleotide sequences of the VGAM556 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM556 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM556 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM556 are further described hereinbelow with reference to Table 1.

[24246] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM556 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM556 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24247] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM556 gene, herein designated VGAM is inhibition of expression of VGAM556 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM556 correlate with, and may be deduced from, the identity of the target genes which VGAM556 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24248] V-abl Abelson Murine Leukemia Viral Oncogene Homolog 2 (arg, Abelson-related gene) (ABL2, Accession NM\_007314) is a VGAM556 host target gene. ABL2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ABL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABL2 BINDING SITE, designated SEQ ID:14229, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24249] A function of VGAM556 is therefore inhibition of V-abl Abelson Murine Leukemia Viral Oncogene Homolog 2 (arg, Abelson-related gene) (ABL2, Accession NM\_007314), a gene which Cytoplasmic tyrosine kinase of the Abelson subfamily. Accordingly, utilities of VGAM556 include di-

agnosis, prevention and treatment of diseases and clinical conditions associated with ABL2. The function of ABL2 has been established by previous studies. Kruh et al. (1986) identified a novel oncogene related to ABL (OMIM Ref. No. 189980) in DNA sequences from human plasma. The new sequence, called ARG by the authors, was localized by in situ hybridization and somatic cell analysis to human chromosome 1q24–q25. The detection of a novel 12–kb transcript from this gene in human normal and tumor cells establishes it as a new member of the tyrosine kinase family that is closely related to but distinct from ABL. A constitutional fragile site is located at 1q24–q25. Seldin and Kruh (1989) mapped the mouse homolog (Abll) to chromosome 1 by analysis of segregation with other distal chromosome 1 genetic polymorphisms in a panel of DNAs from interspecific backcross mice. This defined a region of distal mouse chromosome 1 homologous with human chromosome 1q21–q32.

[24250] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24251] Kruh, G. D.; King, C. R.; Kraus, M. H.; Popescu, N. C.; Amsbaugh, S. C.; McBride, W. O.; Aaronson, S. A. : A novel

human gene closely related to the abl proto-oncogene.

Science 234: 1545–1548, 1986. ; and

[24252] Seldin, M. F.; Kruh, G. D. : Mapping of Abl within a conserved linkage group on distal mouse chromosome 1 syntenic with human chromosome 1 using an interspecific cross. Genomics 4: 221–.

[24253] Further studies establishing the function and utilities of ABL2 are found in John Hopkins OMIM database record ID 164690, and in cited publications numbered 10900–10901, 1103 and 11040 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ATP Synthase, H<sup>+</sup> Transporting, Mitochondrial F<sub>0</sub> Complex, Subunit F6 (ATP5J, Accession NM\_001685) is another VGAM556 host target gene. ATP5J BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ATP5J, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP5J BINDING SITE, designated SEQ ID:7406, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24254] Another function of VGAM556 is therefore inhibition of

ATP Synthase, H<sup>+</sup> Transporting, Mitochondrial F0 Complex, Subunit F6 (ATP5J, Accession NM\_001685), a gene which is one of the chains of the nonenzymatic component of the mitochondrial ATPase complex. Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP5J. The function of ATP5J has been established by previous studies. H<sup>(+)</sup>-ATP synthase is a multisubunit membrane-bound enzyme complex consisting of an F0 segment embedded in the membrane and an F1 segment attached to the F0. The F1 segment provides the catalytic activity for the interconversion of ADP and ATP, whereas the F0 segment contains a proton channel that couples the transmembrane H<sup>+</sup> gradient and membrane potential generated by electron transport to the synthesis of ATP in the F1 domain. Coupling factor 6 (F6) is a soluble integral component of mitochondrial ATP synthase that is required for the interactions of the catalytic and proton-translocating segments. Higuti et al. (1991) and Javed et al. (1991) independently isolated a cDNA encoding F6, or ATP5J, from human kidney and human fetal muscle cDNA libraries, respectively. The deduced protein consists of a 32-amino acid import signal peptide and a mature



76-amino acid polypeptide with an estimated molecular mass of 8,969 Da. Javed et al. (1991) and Higuti et al. (1991) noted that the predicted import signal peptide is rich in basic amino acids, devoid of acidic amino acids, and amphiphilic, which allows it to be water-soluble yet capable of passage through the phospholipid membrane bilayers. The authors reported that the mature human F6 protein has 81% sequence identity with bovine F6, and Higuti et al. (1991) stated that human F6 shares 72% sequence identity with rat F6.

[24255] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24256] Higuti, T.; Tsurumi, C.; Kawamura, Y.; Tsujita, H.; Osaka, F.; Yoshihara, Y.; Tani, I.; Tanaka, K.; Ichihara, A. : Molecular cloning of cDNA for the import precursor of human coupling factor 6 of H(+)-ATP synthase in mitochondria. Biochem. Biophys. Res. Commun. 178: 793-799, 1991. ; and

[24257] Javed, A. A.; Ogata, K.; Sanadi, D. R. : Human mitochondrial ATP synthase: cloning cDNA for the nuclear-encoded precursor of coupling factor 6. Gene 97: 307-310, 1991.

[24258] Further studies establishing the function and utilities of

ATP5J are found in John Hopkins OMIM database record ID 603152, and in cited publications numbered 5432–5434 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cadherin 6, Type 2, K-cadherin (fetal kidney) (CDH6, Accession NM\_004932) is another VGAM556 host target gene. CDH6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CDH6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDH6 BINDING SITE, designated SEQ ID:11374, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24259] Another function of VGAM556 is therefore inhibition of Cadherin 6, Type 2, K-cadherin (fetal kidney) (CDH6, Accession NM\_004932), a gene which is a calcium dependent cell adhesion protein. Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH6. The function of CDH6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference

to VGAM60.Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_004022) is another VGAM556 host target gene. DMD BINDING SITE1 through DMD BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DMD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DMD BINDING SITE1 through DMD BINDING SITE3, designated SEQ ID:10233, SEQ ID:10194 and SEQ ID:10221 respectively, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24260] Another function of VGAM556 is therefore inhibition of Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_004022), a gene which muscular dystrophy . Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DMD. The function of DMD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM218.Neuregulin 2 (NRG2, Accession NM\_004883) is

another VGAM556 host target gene. NRG2 BINDING SITE1 through NRG2 BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by NRG2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRG2 BINDING SITE1 through NRG2 BINDING SITE6, designated SEQ ID:11318, SEQ ID:15144, SEQ ID:15143, SEQ ID:15145, SEQ ID:15146 and SEQ ID:15147 respectively, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24261] Another function of VGAM556 is therefore inhibition of Neuregulin 2 (NRG2, Accession NM\_004883), a gene which recruits erbb1 and erbb2 coreceptors resulting in ligand-stimulated tyrosine phosphorylation and activation of the erbb receptors. Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRG2. The function of NRG2 has been established by previous studies. Neuregulins are a family of growth and differentiation factors that are related to epidermal growth factor (EGF; 131530). The receptors for neuregulins are the ERBB fam-

ily of tyrosine kinase transmembrane receptors, which includes the EGF receptor (EGFR; 131550), ERBB2 (OMIM Ref. No. 164870), ERBB3 (OMIM Ref. No. 190151), and ERBB4 (OMIM Ref. No. 600543). Through interaction with ERBB receptors, neuregulins induce the growth and differentiation of epithelial, neuronal, glial, and other types of cells (Burden and Yarden, 1997). In particular, the neuregulin-ERBB signaling pathways play crucial roles in regulating the proliferation and differentiation of Schwann cells, the myelin-forming cells in the peripheral nervous system. For additional information about neuregulins, see NRG1 (OMIM Ref. No. 142445). Using homologous mouse cDNA as probe, Busfield et al. (1997) cloned 2 NRG2 variants, which they called DON-1r and DON-1b, from a human fetal brain library. The clones predict mosaic proteins containing an N-terminal domain, an immunoglobulin-C2 loop, an EGF-like domain, a transmembrane sequence, and a large cytoplasmic tail showing a number of potential N-linked and O-linked glycosylation sites. DON-1b differs from DON-1r by an 8-amino acid insertion proximal to the transmembrane domain. Northern blot analysis of adult human tissues revealed expression of 3- and 4-kb transcripts restricted to the cerebellum. Expression was

also detected in fetal brain and lung. In situ hybridization of mouse brain sections revealed restricted expression in the cerebellum and dentate gyrus.

[24262] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24263] Burden, S.; Yarden, Y. : Neuregulins and their receptors: a versatile signaling module in organogenesis and oncogenesis. *Neuron* 18: 847–855, 1997. ; and

[24264] Busfield, S. J.; Michnick, D. A.; Chickering, T. W.; Revett, T. L.; Ma, J.; Woolf, E. A.; Comrack, C. A.; Dussault, B. J.; Woolf, J.; Goodearl, A. D. J.; Gearing, D. P. : Characterizati.

[24265] Further studies establishing the function and utilities of NRG2 are found in John Hopkins OMIM database record ID 603818, and in cited publications numbered 4913–4918 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ10748

(Accession NM\_018203) is another VGAM556 host target gene. FLJ10748 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ10748, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu–

cleotide sequences of FLJ10748 BINDING SITE, designated SEQ ID:20086, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24266] Another function of VGAM556 is therefore inhibition of FLJ10748 (Accession NM\_018203). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10748. FLJ10925 (Accession NM\_018275) is another VGAM556 host target gene. FLJ10925 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10925, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10925 BINDING SITE, designated SEQ ID:20259, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24267] Another function of VGAM556 is therefore inhibition of FLJ10925 (Accession NM\_018275). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10925. FLJ20315 (Accession NM\_017763) is another VGAM556

host target gene. FLJ20315 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20315, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20315 BINDING SITE, designated SEQ ID:19379, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24268] Another function of VGAM556 is therefore inhibition of FLJ20315 (Accession NM\_017763). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20315. Leucine-rich Repeat LGI Family, Member 3 (LGI3, Accession NM\_139278) is another VGAM556 host target gene. LGI3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LGI3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LGI3 BINDING SITE, designated SEQ ID:29279, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.



[24269] Another function of VGAM556 is therefore inhibition of Leucine-rich Repeat LIG Family, Member 3 (LIG3, Accession NM\_139278). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LIG3. MAP Kinase-interacting Serine/threonine Kinase 1 (MKNK1, Accession NM\_003684) is another VGAM556 host target gene. MKNK1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MKNK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MKNK1 BINDING SITE, designated SEQ ID:9792, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24270] Another function of VGAM556 is therefore inhibition of MAP Kinase-interacting Serine/threonine Kinase 1 (MKNK1, Accession NM\_003684). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MKNK1. PM5 (Accession XM\_027359) is another VGAM556 host target gene. PM5 BINDING SITE is HOST TARGET binding

site found in the 5` untranslated region of mRNA encoded by PM5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PM5 BINDING SITE, designated SEQ ID:30497, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24271] Another function of VGAM556 is therefore inhibition of PM5 (Accession XM\_027359). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PM5. Protein Tyrosine Phosphatase, Non-receptor Type 4 (megakaryocyte) (PTPN4, Accession NM\_002830) is another VGAM556 host target gene. PTPN4 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PTPN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPN4 BINDING SITE, designated SEQ ID:8707, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24272] Another function of VGAM556 is therefore inhibition of Protein Tyrosine Phosphatase, Non-receptor Type 4 (megakaryocyte) (PTPN4, Accession NM\_002830). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPN4. LOC145748 (Accession XM\_096853) is another VGAM556 host target gene. LOC145748 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145748, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145748 BINDING SITE, designated SEQ ID:40579, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24273] Another function of VGAM556 is therefore inhibition of LOC145748 (Accession XM\_096853). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145748. LOC151445 (Accession XM\_045283) is another VGAM556 host target gene. LOC151445 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151445, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151445 BINDING SITE, designated SEQ ID:34419, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24274] Another function of VGAM556 is therefore inhibition of LOC151445 (Accession XM\_045283). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151445. LOC163682 (Accession XM\_099402) is another VGAM556 host target gene. LOC163682 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC163682, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163682 BINDING SITE, designated SEQ ID:42096, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24275] Another function of VGAM556 is therefore inhibition of LOC163682 (Accession XM\_099402). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC163682. LOC197003 (Accession XM\_113798) is another VGAM556 host target gene. LOC197003 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197003, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197003 BINDING SITE, designated SEQ ID:42444, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24276] Another function of VGAM556 is therefore inhibition of LOC197003 (Accession XM\_113798). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197003. LOC221975 (Accession XM\_166534) is another VGAM556 host target gene. LOC221975 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221975, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221975 BINDING SITE, designated SEQ ID:44495, to

the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24277] Another function of VGAM556 is therefore inhibition of LOC221975 (Accession XM\_166534). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221975. LOC254712 (Accession XM\_171104) is another VGAM556 host target gene. LOC254712 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254712, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254712 BINDING SITE, designated SEQ ID:45912, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24278] Another function of VGAM556 is therefore inhibition of LOC254712 (Accession XM\_171104). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254712. LOC93538 (Accession XM\_051927) is another VGAM556 host target gene. LOC93538 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC93538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93538 BINDING SITE, designated SEQ ID:35923, to the nucleotide sequence of VGAM556 RNA, herein designated VGAM RNA, also designated SEQ ID:3267.

[24279] Another function of VGAM556 is therefore inhibition of LOC93538 (Accession XM\_051927). Accordingly, utilities of VGAM556 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93538. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 557 (VGAM557) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24280] VGAM557 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM557 was detected is described hereinabove with reference to Figs. 1–8.

[24281] VGAM557 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Spodoptera Exigua Nucleopolyhedrovirus. VGAM557 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24282] VGAM557 gene encodes a VGAM557 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM557 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM557 precursor RNA is designated SEQ ID:543, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:543 is located at position 77506 relative to the genome of Spodoptera Exigua Nucleopolyhedrovirus.

[24283] VGAM557 precursor RNA folds onto itself, forming VGAM557 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.



[24284] An enzyme complex designated DICER COMPLEX, `dices` the VGAM557 folded precursor RNA into VGAM557 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM557 RNA is designated SEQ ID:3268, and is provided hereinbelow with reference to the sequence listing part.

[24285] VGAM557 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM557 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM557 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24286] VGAM557 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM557 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM557 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM557 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM557 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24287] The complementary binding of VGAM557 RNA, herein designated VGAM RNA, to host target binding sites on VGAM557 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM557 host tar-

get RNA into VGAM557 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24288] It is appreciated that VGAM557 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM557 host target genes. The mRNA of each one of this plurality of VGAM557 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM557 RNA, herein designated VGAM RNA, and which when bound by VGAM557 RNA causes inhibition of translation of respective one or more VGAM557 host target proteins.

[24289] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM557 gene, herein designated VGAM GENE, on one or more VGAM557 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24290] It is yet further appreciated that a function of VGAM557 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM557 include diagnosis, prevention and treatment of viral infection by Spodoptera Exigua Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM557 correlate with, and may be deduced from, the identity of the host target genes which VGAM557 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24291] Nucleotide sequences of the VGAM557 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM557 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM557 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM557 are further

described hereinbelow with reference to Table 1.

[24292] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM557 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM557 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24293] As mentioned hereinabove with reference to Fig. 1, a function of VGAM557 gene, herein designated VGAM is inhibition of expression of VGAM557 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM557 correlate with, and may be deduced from, the identity of the target genes which VGAM557 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24294] Phosphatase, Orphan 1 (phospho1, Accession XM\_091572) is a VGAM557 host target gene. phospho1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by phospho1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of phospho1 BINDING SITE, designated SEQ ID:40063, to the nucleotide sequence of VGAM557 RNA, herein designated VGAM RNA, also designated SEQ ID:3268.

[24295] A function of VGAM557 is therefore inhibition of Phosphatase, Orphan 1 (phospho1, Accession XM\_091572). Accordingly, utilities of VGAM557 include diagnosis, prevention and treatment of diseases and clinical conditions associated with phospho1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 558 (VGAM558) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24296] VGAM558 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM558 was detected is described hereinabove with reference to Figs. 1–8.

[24297] VGAM558 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Spodoptera Exigua Nucleopolyhedrovirus. VGAM558 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene

contained in the human genome.

[24298] VGAM558 gene encodes a VGAM558 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM558 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM558 precursor RNA is designated SEQ ID:544, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:544 is located at position 78942 relative to the genome of Spodoptera Exigua Nucleopolyhedrovirus.

[24299] VGAM558 precursor RNA folds onto itself, forming VGAM558 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24300] An enzyme complex designated DICER COMPLEX, `dices` the VGAM558 folded precursor RNA into VGAM558 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM558 RNA is designated SEQ ID:3269, and is provided hereinbelow with reference to the sequence listing part.

[24301] VGAM558 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM558 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM558 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24302] VGAM558 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM558 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM558 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-



quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM558 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM558 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24303] The complementary binding of VGAM558 RNA, herein designated VGAM RNA, to host target binding sites on VGAM558 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM558 host target RNA into VGAM558 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24304] It is appreciated that VGAM558 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM558 host target genes. The mRNA of each one of this plurality of VGAM558 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM558 RNA, herein designated VGAM RNA, and which when bound by VGAM558 RNA causes inhibition of translation of respective one or more VGAM558 host target proteins.

[24305] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM558 gene, herein designated VGAM GENE, on one or more VGAM558 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24306] It is yet further appreciated that a function of VGAM558 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of viral infection by Spodoptera Exigua Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM558 correlate with, and may be deduced from, the identity of the host target genes which VGAM558 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24307] Nucleotide sequences of the VGAM558 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM558 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM558 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM558 are further described hereinbelow with reference to Table 1.

[24308] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM558 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM558 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24309] As mentioned hereinabove with reference to Fig. 1, a function of VGAM558 gene, herein designated VGAM is inhibition of expression of VGAM558 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM558 correlate with, and may be deduced from, the identity of the target genes which VGAM558 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24310] Activating Transcription Factor 7 (ATF7, Accession NM\_006856) is a VGAM558 host target gene. ATF7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATF7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATF7 BINDING SITE, designated SEQ ID:13727, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24311] A function of VGAM558 is therefore inhibition of Activating Transcription Factor 7 (ATF7, Accession NM\_006856). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATF7. Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104) is another VGAM558 host target gene. BACE BINDING SITE1 and BACE BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by BACE, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACE BINDING SITE1 and BACE BINDING SITE2, designated SEQ ID:14422 and SEQ ID:29090 respectively, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24312] Another function of VGAM558 is therefore inhibition of Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104), a gene which is responsible for the proteolytic processing of the amyloid precursor protein. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACE. The function of BACE and its associa-

tion with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM173. Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051) is another VGAM558 host target gene. EGLN1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EGLN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGLN1 BINDING SITE, designated SEQ ID:22583, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24313] Another function of VGAM558 is therefore inhibition of Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051), a gene which is expressed in the cytoplasm of arterial smooth muscle cells. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN1. The function of EGLN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM216. Fibroblast Growth Factor 2 (basic) (FGF2, Ac-

cession NM\_002006) is another VGAM558 host target gene. FGF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FGF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF2 BINDING SITE, designated SEQ ID:7743, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24314] Another function of VGAM558 is therefore inhibition of Fibroblast Growth Factor 2 (basic) (FGF2, Accession NM\_002006), a gene which probably involved in nervous system development and function. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF2. The function of FGF2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM51. Gap Junction Protein, Alpha 1, 43kDa (connexin 43) (GJA1, Accession NM\_000165) is another VGAM558 host target gene. GJA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GJA1, corresponding to a HOST TARGET bind-

ing site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GJA1 BINDING SITE, designated SEQ ID:5680, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24315] Another function of VGAM558 is therefore inhibition of Gap Junction Protein, Alpha 1, 43kDa (connexin 43) (GJA1, Accession NM\_000165), a gene which may act in synchronizing heart contraction and embryonic development. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GJA1. The function of GJA1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM341. Heparanase (HPSE, Accession NM\_006665) is another VGAM558 host target gene. HPSE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HPSE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HPSE BINDING SITE, designated SEQ ID:13481,



to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24316] Another function of VGAM558 is therefore inhibition of Heparanase (HPSE, Accession NM\_006665), a gene which is an endoglycosidase that cleaves heparan sulfate. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HPSE. The function of HPSE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM374. Mannosyl (alpha-1,6-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession NM\_002408) is another VGAM558 host target gene. MGAT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGAT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAT2 BINDING SITE, designated SEQ ID:8234, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24317] Another function of VGAM558 is therefore inhibition of Mannosyl (alpha-1,6-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession NM\_002408). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGAT2. Myeloid/lymphoid Or Mixed-lineage Leukemia (trithorax homolog, Drosophila); Translocated To, 2 (MLLT2, Accession NM\_005935) is another VGAM558 host target gene. MLLT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MLLT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MLLT2 BINDING SITE, designated SEQ ID:12573, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24318] Another function of VGAM558 is therefore inhibition of Myeloid/lymphoid Or Mixed-lineage Leukemia (trithorax homolog, Drosophila); Translocated To, 2 (MLLT2, Accession NM\_005935), a gene which is a Putative transcription factor. Accordingly, utilities of VGAM558 include diagno-

sis, prevention and treatment of diseases and clinical conditions associated with MLLT2. The function of MLLT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM57. Nuclear Receptor Coactivator 6 Interacting Protein (NCOA6IP, Accession NM\_024831) is another VGAM558 host target gene. NCOA6IP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCOA6IP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA6IP BINDING SITE, designated SEQ ID:24228, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24319] Another function of VGAM558 is therefore inhibition of Nuclear Receptor Coactivator 6 Interacting Protein (NCOA6IP, Accession NM\_024831). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA6IP. RAS P21 Protein Activator (GTPase activating protein) 1 (RASA1, Accession NM\_022650) is another

VGAM558 host target gene. RASA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RASA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASA1 BINDING SITE, designated SEQ ID:22906, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24320] Another function of VGAM558 is therefore inhibition of RAS P21 Protein Activator (GTPase activating protein) 1 (RASA1, Accession NM\_022650), a gene which is involved in the control of cellular proliferation and differentiation. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASA1. The function of RASA1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM464. Ribonuclease, RNase A Family, 4 (RNASE4, Accession NM\_002937) is another VGAM558 host target gene. RNASE4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNASE4, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNASE4 BINDING SITE, designated SEQ ID:8838, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24321] Another function of VGAM558 is therefore inhibition of Ribonuclease, RNase A Family, 4 (RNASE4, Accession NM\_002937). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNASE4. Suppressor of Fused Homolog (Drosophila) (SUFU, Accession NM\_016169) is another VGAM558 host target gene. SUFU BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SUFU, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SUFU BINDING SITE, designated SEQ ID:18259, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24322] Another function of VGAM558 is therefore inhibition of Suppressor of Fused Homolog (Drosophila) (SUFU, Acces-

sion NM\_016169). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SUFU. TSLP (Accession NM\_138551) is another VGAM558 host target gene. TSLP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TSLP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSLP BINDING SITE, designated SEQ ID:28849, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24323] Another function of VGAM558 is therefore inhibition of TSLP (Accession NM\_138551), a gene which may contribute directly to the activation of Langerhans cells and inhibit apoptosis. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSLP. The function of TSLP has been established by previous studies. By EST and genomic database screening for sequences similar to IL7, followed by screening a lung fibroblast sarcoma cDNA library, Reche et al. (2001) obtained a cDNA encoding TSLP. The deduced 159-amino acid protein, which is only 43%

identical to mouse Tslp, contains a 28-residue signal sequence, 6 cysteines, and 2 N-glycosylation sites. SDS-PAGE analysis showed expression of a 23-kD protein, larger than the predicted 15 kD, suggesting that TSLP is glycosylated. PCR analysis of a panel of cDNA libraries and cultured cell lines indicated that expression of a 1.3-kb TSLP transcript may be restricted to a few lung libraries. Reche et al. (2001) also identified TSLP receptor, which is composed of TSLPR (CRLF2; 300357) and IL7R (OMIM Ref. No. 146661) subunits. Dendritic cells (DCs) and monocytes coexpress IL7R and TSLPR. Quentmeier et al. (2001) also cloned and characterized TSLP. They noted the presence of 7 basic C-terminal amino acids (KKRRKRK) in the protein and that 6 of the 7 cysteines in the mouse protein (those involved in disulfide bond formation) are conserved in human, whereas the sites for N-glycosylation are distinct. Northern blot analysis revealed wide expression of an approximately 1.1-kb transcript, with highest levels in heart, liver, testis, and prostate. Reche et al. (2001) showed that incubation of DCs or monocytes with TSLP enhanced the expression of CCL17 (OMIM Ref. No. 601520), CCL18 (OMIM Ref. No. 603757), CCL22 (OMIM Ref. No. 602957), and CCL19 (OMIM Ref. No. 602227).

IL7, on the other hand, induced expression of CCL17, CCL22, and CCL19, but also CXCL8 (OMIM Ref. No. 146930), CXCL7 (OMIM Ref. No. 121010), CXCL5 (OMIM Ref. No. 600324), CXCL1 (OMIM Ref. No. 155730), CXCL2 (OMIM Ref. No. 139110), and CXCL3 (OMIM Ref. No. 139111). Functional analysis indicated that TSLP enhances the DC maturation process, as evidenced by upregulation of DC markers and costimulatory molecules and stronger T-cell proliferation. By screening myeloid cell lines, Quentmeier et al. (2001) established that an acute myeloid leukemia line, MUTZ-3, responds by proliferating in response to TSLP. TSLP also inhibited apoptosis in these cells. Proliferation in response to TSLP could not be attributed to the production of other growth factors tested and could be inhibited by relatively high concentrations of anti-IL7R. TSLP, like IL7, stimulated phosphorylation of STAT5 (OMIM Ref. No. 601511), but unlike IL7, it did not activate JAK3 (OMIM Ref. No. 600173). TSLP did not phosphorylate mitogen-activated protein kinases (e.g., ERK1; 601795). By flow cytometric analysis, Soumelis et al. (2002) showed that TSLP-activated DCs (TSLP-DCs) express higher levels of HLA-DR and DCLAMP (OMIM Ref. No. 605883) than do nonactivated or IL7-activated DCs,



and that TSLP–DCs induce marked proliferation and expansion of allogeneic naive CD4 (OMIM Ref. No. 186940)–positive T cells. Quantitative mRNA screening and ELISA analysis showed that TSLP–DCs do not produce detectable proinflammatory cytokines, but do produce high levels of TARC (CCL17) and MDC (CCL22) chemokines, which preferentially attract CCR4 (OMIM Ref. No. 604836)–expressing Th2 lymphocytes. TSLP–DCs induced CD4 cells to produce high amounts of IL13 (OMIM Ref. No. 147683), IL5 (OMIM Ref. No. 147850), and the proinflammatory cytokine tumor necrosis factor (TNF; 191160), but only low amounts of IL10 (OMIM Ref. No. 124092) and gamma–interferon (IFNG; 147570). RT–PCR analysis did not detect TSLP in most hemopoietic cells, the exception being mast cells. Keratinocytes, epithelial cells, smooth muscle cells, and lung fibroblasts also expressed high levels of TSLP. Within tonsils, highest levels were in crypt epithelial cells. Soumelis et al. (2002) suggested that TSLP may contribute to constitutive inflammation in this tissue and sporadic inflammation in squamous epithelium. Immunohistochemical analysis of allergic inflammatory tissue showed high expression of TSLP in keratinocytes of acute and chronic atopic dermatitis lesions, but no ex–

pression in normal skin. Strong TSLP expression in atopic dermatitis was associated with the disappearance of langerin (OMIM Ref. No. 604862)–positive Langerhans cells within the epidermis and the concurrent appearance of many DCLAMP–activated DCs within the dermis, many of which expressed langerin. Soumelis et al. (2002) proposed that TSLP expression by keratinocytes in atopic dermatitis lesions may contribute directly to the activation of Langerhans cells, which may migrate into the dermis and then the draining lymph nodes where they can prime allergen–specific Th2 responses.

[24324] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24325] Reche, P. A.; Soumelis, V.; Gorman, D. M.; Clifford, T.; Liu, M.; Travis, M.; Zurawski, S. M.; Johnston, J.; Liu, Y.–J.; Spits, H.; de Waal Malefyt, R.; Kastelein, R. A.; Bazan, J. F. : Human thymic stromal lymphopoietin preferentially stimulates myeloid cells. *J. Immun.* 167: 336–343, 2001. ; and

[24326] Soumelis, V.; Reche, P. A.; Kanzler, H.; Yuan, W.; Edward, G.; Homey, B.; Gilliet, M.; Ho, S.; Antonenko, S.; Lauerma, A.; Smith, K.; Gorman, D.; Zurawski, S.; Abrams, J.; Menon, S.; Mc.

[24327] Further studies establishing the function and utilities of TSLP are found in John Hopkins OMIM database record ID 607003, and in cited publications numbered 555 and 6729 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ubiquitin-like 1 (sentrin) (UBL1, Accession NM\_003352) is another VGAM558 host target gene. UBL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBL1 BINDING SITE, designated SEQ ID:9378, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24328] Another function of VGAM558 is therefore inhibition of Ubiquitin-like 1 (sentrin) (UBL1, Accession NM\_003352), a gene which generates proteins resistant to degradation through its modification. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBL1. The function of UBL1 and its association with various diseases and clinical conditions, has been established by previous

studies, as described hereinabove with reference to VGAM206. Von Hippel–Lindau Syndrome (VHL, Accession NM\_000551) is another VGAM558 host target gene. VHL BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by VHL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VHL BINDING SITE, designated SEQ ID:6161, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24329] Another function of VGAM558 is therefore inhibition of Von Hippel–Lindau Syndrome (VHL, Accession NM\_000551), a gene which may control rna stability through the selective degradation of rna-bound proteins. Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VHL. The function of VHL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM197. ADP-ribosylation Factor Domain Protein 1, 64kDa (ARFD1, Accession NM\_001656) is another VGAM558 host target gene.

ARFD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARFD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARFD1 BINDING SITE, designated SEQ ID:7375, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24330] Another function of VGAM558 is therefore inhibition of ADP-ribosylation Factor Domain Protein 1, 64kDa (ARFD1, Accession NM\_001656). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARFD1. Bromodomain Containing 4 (BRD4, Accession NM\_014299) is another VGAM558 host target gene. BRD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BRD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BRD4 BINDING SITE, designated SEQ ID:15595, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA,

also designated SEQ ID:3269.

[24331] Another function of VGAM558 is therefore inhibition of Bromodomain Containing 4 (BRD4, Accession NM\_014299). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BRD4. DJ667H12.2 (Accession NM\_019605) is another VGAM558 host target gene. DJ667H12.2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DJ667H12.2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DJ667H12.2 BINDING SITE, designated SEQ ID:21218, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24332] Another function of VGAM558 is therefore inhibition of DJ667H12.2 (Accession NM\_019605). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DJ667H12.2. DKFZp547I224 (Accession NM\_020221) is another VGAM558 host target gene. DKFZp547I224 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by DKFZp547I224, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547I224 BINDING SITE, designated SEQ ID:21476, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24333] Another function of VGAM558 is therefore inhibition of DKFZp547I224 (Accession NM\_020221). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547I224. DKFZP566K1924 (Accession XM\_057469) is another VGAM558 host target gene. DKFZP566K1924 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP566K1924, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566K1924 BINDING SITE, designated SEQ ID:36523, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24334] Another function of VGAM558 is therefore inhibition of DKFZP566K1924 (Accession XM\_057469). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566K1924. DKFZP586C1619 (Accession XM\_030350) is another VGAM558 host target gene. DKFZP586C1619 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP586C1619, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586C1619 BINDING SITE, designated SEQ ID:31019, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24335] Another function of VGAM558 is therefore inhibition of DKFZP586C1619 (Accession XM\_030350). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586C1619. DRCTNNB1A (Accession NM\_032581) is another VGAM558 host target gene. DRCTNNB1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by



DRCTNNB1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRCTNNB1A BINDING SITE, designated SEQ ID:26317, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24336] Another function of VGAM558 is therefore inhibition of DRCTNNB1A (Accession NM\_032581). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRCTNNB1A. ELL2 (Accession NM\_012081) is another VGAM558 host target gene. ELL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ELL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELL2 BINDING SITE, designated SEQ ID:14369, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24337] Another function of VGAM558 is therefore inhibition of ELL2 (Accession NM\_012081). Accordingly, utilities of

VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELL2.

FLJ10199 (Accession XM\_048840) is another VGAM558 host target gene. FLJ10199 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10199, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10199 BINDING SITE, designated SEQ ID:35286, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24338] Another function of VGAM558 is therefore inhibition of FLJ10199 (Accession XM\_048840). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10199. FLJ12650 (Accession NM\_024522) is another VGAM558 host target gene. FLJ12650 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12650 BINDING SITE,

designated SEQ ID:23723, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24339] Another function of VGAM558 is therefore inhibition of FLJ12650 (Accession NM\_024522). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12650. FLJ13189 (Accession NM\_024882) is another VGAM558 host target gene. FLJ13189 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13189, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13189 BINDING SITE, designated SEQ ID:24333, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24340] Another function of VGAM558 is therefore inhibition of FLJ13189 (Accession NM\_024882). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13189. FLJ14054 (Accession NM\_024563) is another VGAM558 host target gene. FLJ14054 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ14054, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14054 BINDING SITE, designated SEQ ID:23786, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24341] Another function of VGAM558 is therefore inhibition of FLJ14054 (Accession NM\_024563). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14054. FLJ20093 (Accession NM\_017664) is another VGAM558 host target gene. FLJ20093 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20093, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20093 BINDING SITE, designated SEQ ID:19205, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24342] Another function of VGAM558 is therefore inhibition of

FLJ20093 (Accession NM\_017664). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20093. FLJ20793 (Accession XM\_166296) is another VGAM558 host target gene. FLJ20793 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20793, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20793 BINDING SITE, designated SEQ ID:44111, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24343] Another function of VGAM558 is therefore inhibition of FLJ20793 (Accession XM\_166296). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20793. KIAA0367 (Accession XM\_041018) is another VGAM558 host target gene. KIAA0367 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0367, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0367 BINDING SITE, designated SEQ ID:33419, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24344] Another function of VGAM558 is therefore inhibition of KIAA0367 (Accession XM\_041018). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0367. Nuclear Factor of Activated T-cells 5, Tonicity-responsive (NFAT5, Accession NM\_006599) is another VGAM558 host target gene. NFAT5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NFAT5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFAT5 BINDING SITE, designated SEQ ID:13378, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24345] Another function of VGAM558 is therefore inhibition of Nuclear Factor of Activated T-cells 5, Tonicity-responsive (NFAT5, Accession NM\_006599). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with NFAT5. PRO1386 (Accession NM\_031269) is another VGAM558 host target gene. PRO1386 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO1386, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1386 BINDING SITE, designated SEQ ID:25293, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24346] Another function of VGAM558 is therefore inhibition of PRO1386 (Accession NM\_031269). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1386. RRN3 (Accession NM\_018427) is another VGAM558 host target gene. RRN3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RRN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RRN3 BINDING SITE, designated SEQ ID:20490, to the nucleotide sequence of VGAM558 RNA,

herein designated VGAM RNA, also designated SEQ ID:3269.

[24347] Another function of VGAM558 is therefore inhibition of RRN3 (Accession NM\_018427). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RRN3. Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession NM\_033285) is another VGAM558 host target gene. TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TP53INP1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2, designated SEQ ID:27107 and SEQ ID:36117 respectively, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24348] Another function of VGAM558 is therefore inhibition of Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession NM\_033285). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TP53INP1.



LOC120892 (Accession XM\_058513) is another VGAM558 host target gene. LOC120892 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120892, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120892 BINDING SITE, designated SEQ ID:36649, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24349] Another function of VGAM558 is therefore inhibition of LOC120892 (Accession XM\_058513). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120892. LOC130612 (Accession XM\_059461) is another VGAM558 host target gene. LOC130612 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC130612, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130612 BINDING SITE, designated SEQ ID:36998, to the nucleotide sequence of VGAM558 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3269.

[24350] Another function of VGAM558 is therefore inhibition of LOC130612 (Accession XM\_059461). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130612. LOC145828 (Accession XM\_096879) is another VGAM558 host target gene. LOC145828 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145828, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145828 BINDING SITE, designated SEQ ID:40613, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24351] Another function of VGAM558 is therefore inhibition of LOC145828 (Accession XM\_096879). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145828. LOC147341 (Accession XM\_097223) is another VGAM558 host target gene. LOC147341 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147341, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147341 BINDING SITE, designated SEQ ID:40828, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24352] Another function of VGAM558 is therefore inhibition of LOC147341 (Accession XM\_097223). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147341. LOC149175 (Accession XM\_086445) is another VGAM558 host target gene. LOC149175 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149175, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149175 BINDING SITE, designated SEQ ID:38660, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24353] Another function of VGAM558 is therefore inhibition of LOC149175 (Accession XM\_086445). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC149175. LOC149650 (Accession XM\_086623) is another VGAM558 host target gene. LOC149650 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149650 BINDING SITE, designated SEQ ID:38797, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24354] Another function of VGAM558 is therefore inhibition of LOC149650 (Accession XM\_086623). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149650. LOC152762 (Accession XM\_087518) is another VGAM558 host target gene. LOC152762 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152762, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152762 BINDING SITE, designated SEQ ID:39308, to

the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24355] Another function of VGAM558 is therefore inhibition of LOC152762 (Accession XM\_087518). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152762. LOC196528 (Accession XM\_113745) is another VGAM558 host target gene. LOC196528 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196528, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196528 BINDING SITE, designated SEQ ID:42406, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24356] Another function of VGAM558 is therefore inhibition of LOC196528 (Accession XM\_113745). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196528. LOC221876 (Accession XM\_168220) is another VGAM558 host target gene. LOC221876 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC221876, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221876 BINDING SITE, designated SEQ ID:45080, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24357] Another function of VGAM558 is therefore inhibition of LOC221876 (Accession XM\_168220). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221876. LOC254042 (Accession XM\_171022) is another VGAM558 host target gene. LOC254042 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254042, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254042 BINDING SITE, designated SEQ ID:45794, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24358] Another function of VGAM558 is therefore inhibition of LOC254042 (Accession XM\_171022). Accordingly, utilities

of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254042. LOC255446 (Accession XM\_173154) is another VGAM558 host target gene. LOC255446 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC255446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255446 BINDING SITE, designated SEQ ID:46409, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24359] Another function of VGAM558 is therefore inhibition of LOC255446 (Accession XM\_173154). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255446. LOC257017 (Accession XM\_173227) is another VGAM558 host target gene. LOC257017 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC257017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC257017 BINDING SITE, designated SEQ ID:46500, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24360] Another function of VGAM558 is therefore inhibition of LOC257017 (Accession XM\_173227). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257017. LOC51644 (Accession NM\_016057) is another VGAM558 host target gene. LOC51644 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51644, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51644 BINDING SITE, designated SEQ ID:18132, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24361] Another function of VGAM558 is therefore inhibition of LOC51644 (Accession NM\_016057). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51644. LOC92360 (Accession XM\_044589) is another VGAM558 host target gene. LOC92360 BINDING SITE is



HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92360, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92360 BINDING SITE, designated SEQ ID:34241, to the nucleotide sequence of VGAM558 RNA, herein designated VGAM RNA, also designated SEQ ID:3269.

[24362] Another function of VGAM558 is therefore inhibition of LOC92360 (Accession XM\_044589). Accordingly, utilities of VGAM558 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92360. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 559 (VGAM559) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24363] VGAM559 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM559 was detected is described hereinabove with reference to Figs. 1-8.

[24364] VGAM559 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM559 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24365] VGAM559 gene encodes a VGAM559 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM559 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM559 precursor RNA is designated SEQ ID:545, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:545 is located at position 19237 relative to the genome of Fowlpox Virus.

[24366] VGAM559 precursor RNA folds onto itself, forming VGAM559 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[24367] An enzyme complex designated DICER COMPLEX, `dices` the VGAM559 folded precursor RNA into VGAM559 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM559 RNA is designated SEQ ID:3270, and is provided hereinbelow with reference to the sequence listing part.

[24368] VGAM559 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM559 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM559 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24369] VGAM559 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM559 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM559 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM559 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM559 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24370] The complementary binding of VGAM559 RNA, herein designated VGAM RNA, to host target binding sites on VGAM559 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM559 host target RNA into VGAM559 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24371] It is appreciated that VGAM559 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM559 host target genes. The mRNA of each one of this plurality of VGAM559 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM559 RNA, herein designated VGAM RNA, and which when bound by VGAM559 RNA causes inhibition of translation of respective one or more VGAM559 host target proteins.

[24372] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM559 gene, herein designated VGAM GENE, on one or more VGAM559 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24373] It is yet further appreciated that a function of VGAM559 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM559 correlate with, and may be deduced from, the identity of the host target genes which VGAM559 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24374] Nucleotide sequences of the VGAM559 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM559 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM559 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM559 are further described hereinbelow with reference to Table 1.

[24375] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM559 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM559 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24376] As mentioned hereinabove with reference to Fig. 1, a function of VGAM559 gene, herein designated VGAM is inhibition of expression of VGAM559 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM559 correlate with, and may be deduced from, the identity of the target genes which VGAM559 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24377] Dyskeratosis Congenita 1, Dyskerin (DKC1, Accession NM\_001363) is a VGAM559 host target gene. DKC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of DKC1 BINDING SITE, designated SEQ ID:7044, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24378] A function of VGAM559 is therefore inhibition of Dyskeratosis Congenita 1, Dyskerin (DKC1, Accession NM\_001363), a gene which may have cell cycle and nucleolar functions. Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKC1. The function of DKC1 has been established by previous studies. Heiss et al. (1998) demonstrated missense mutations in the DKC1 gene that correlated with dyskeratosis congenita. The disease is characterized by the early manifestation of reticulate skin pigmentation, nail dystrophy, and mucosal leukoplakia. Progressive bone marrow failure occurs in over 80% of cases and is the main cause of early mortality. Variability in the age of onset, severity of bone marrow failure, and range of congenital abnormalities was observed. An increased risk of developing different types of malignancies also exists. Chromosomal instability is indicated by the keratin chromosomal aberrations in skin fibroblast cell cultures and bone marrow metaphases. In



contrast to patients with Fanconi anemia (OMIM Ref. No. 227650), lymphocytes from DKC patients do not show an increased sensitivity to clastogens. Females heterozygous for the mutant gene showed a skewed pattern of X-chromosome inactivation consistent with the gene defect giving rise to a proliferation and/or survival disadvantage in those cells expressing it. By positional cloning, Heiss et al. (1998) identified a gene, symbolized DKC1, in the Xq28 region that is the cause of X-linked recessive dyskeratosis congenita (DKC; 305000). Heiss et al. (1998) found that the DKC1 gene is highly conserved across species barriers and is the ortholog of rat NAP57 and *S. cerevisiae* Cbf5. The gene product, referred to as dyskerin, contains 2 TruB pseudouridine synthase motifs, multiple phosphorylation sites, and a carboxy-terminal lysine-rich domain. By analogy to the function of known dyskerin orthologs, Heiss et al. (1998) predicted that dyskerin is involved in the cell cycle and nucleolar function.

[24379] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24380] Heiss, N. S.; Knight, S. W.; Vulliamy, T. J.; Klauck, S. M.;

Wiemann, S.; Mason, P. J.; Poustka, A.; Dokal, I. : X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. *Nature Genet.* 19: 32–38, 1998. ; and

[24381] Heiss, N. S.; Megarbane, A.; Klauck, S. M.; Kreuz, F. R.; Makhoul, E.; Majewski, F.; Poustka, A. : One novel and two recurrent missense DKC1 mutations in patients with dyskeratosis cong.

[24382] Further studies establishing the function and utilities of DKC1 are found in John Hopkins OMIM database record ID 300126, and in cited publications numbered 9154–915 and 10979–10987 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Glutamate Receptor, Metabotropic 6 (GRM6, Accession NM\_000843) is another VGAM559 host target gene. GRM6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRM6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRM6 BINDING SITE, designated SEQ ID:6513, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24383] Another function of VGAM559 is therefore inhibition of Glutamate Receptor, Metabotropic 6 (GRM6, Accession NM\_000843). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRM6. Nuclear Receptor Coactivator 6 (NCOA6, Accession NM\_014071) is another VGAM559 host target gene. NCOA6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NCOA6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA6 BINDING SITE, designated SEQ ID:15294, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24384] Another function of VGAM559 is therefore inhibition of Nuclear Receptor Coactivator 6 (NCOA6, Accession NM\_014071), a gene which activates gene transcription through ligand-dependent association with coactivators. Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA6. The function of NCOA6 and its association with various diseases and clinical conditions,

has been established by previous studies, as described hereinabove with reference to VGAM25.Solute Carrier Family 11 (proton-coupled divalent metal ion transporters), Member 3 (SLC11A3, Accession NM\_014585) is another VGAM559 host target gene. SLC11A3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC11A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC11A3 BINDING SITE, designated SEQ ID:15943, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24385] Another function of VGAM559 is therefore inhibition of Solute Carrier Family 11 (proton-coupled divalent metal ion transporters), Member 3 (SLC11A3, Accession NM\_014585). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC11A3. ESDN (Accession NM\_080927) is another VGAM559 host target gene. ESDN BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ESDN, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESDN BINDING SITE, designated SEQ ID:28156, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24386] Another function of VGAM559 is therefore inhibition of ESDN (Accession NM\_080927). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESDN. FLJ20445 (Accession NM\_017824) is another VGAM559 host target gene. FLJ20445 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20445, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20445 BINDING SITE, designated SEQ ID:19484, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24387] Another function of VGAM559 is therefore inhibition of FLJ20445 (Accession NM\_017824). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20445.

FLJ23510 (Accession NM\_024720) is another VGAM559 host target gene. FLJ23510 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ23510, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23510 BINDING SITE, designated SEQ ID:24054, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24388] Another function of VGAM559 is therefore inhibition of FLJ23510 (Accession NM\_024720). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23510. KIAA0179 (Accession XM\_035973) is another VGAM559 host target gene. KIAA0179 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0179, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0179 BINDING SITE, designated SEQ ID:32366, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3270.

[24389] Another function of VGAM559 is therefore inhibition of KIAA0179 (Accession XM\_035973). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0179. KIAA1535 (Accession XM\_086565) is another VGAM559 host target gene. KIAA1535 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1535, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1535 BINDING SITE, designated SEQ ID:38769, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24390] Another function of VGAM559 is therefore inhibition of KIAA1535 (Accession XM\_086565). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1535. Kv6.3 (Accession NM\_133490) is another VGAM559 host target gene. Kv6.3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by Kv6.3, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Kv6.3 BINDING SITE, designated SEQ ID:28568, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24391] Another function of VGAM559 is therefore inhibition of Kv6.3 (Accession NM\_133490). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Kv6.3. PFTAIRE Protein Kinase 1 (PFTK1, Accession NM\_012395) is another VGAM559 host target gene. PFTK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PFTK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PFTK1 BINDING SITE, designated SEQ ID:14757, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24392] Another function of VGAM559 is therefore inhibition of PFTAIRE Protein Kinase 1 (PFTK1, Accession NM\_012395). Accordingly, utilities of VGAM559 include diagnosis, pre-



vention and treatment of diseases and clinical conditions associated with PFTK1. LOC139522 (Accession XM\_066738) is another VGAM559 host target gene. LOC139522 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC139522, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC139522 BINDING SITE, designated SEQ ID:37345, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24393] Another function of VGAM559 is therefore inhibition of LOC139522 (Accession XM\_066738). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC139522. LOC196485 (Accession XM\_113731) is another VGAM559 host target gene. LOC196485 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC196485, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC196485 BINDING SITE, designated SEQ ID:42381, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24394] Another function of VGAM559 is therefore inhibition of LOC196485 (Accession XM\_113731). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196485. LOC202986 (Accession XM\_117489) is another VGAM559 host target gene. LOC202986 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202986, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202986 BINDING SITE, designated SEQ ID:43472, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24395] Another function of VGAM559 is therefore inhibition of LOC202986 (Accession XM\_117489). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202986. LOC203378 (Accession XM\_117541) is another VGAM559 host target gene. LOC203378 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC203378, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203378 BINDING SITE, designated SEQ ID:43556, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24396] Another function of VGAM559 is therefore inhibition of LOC203378 (Accession XM\_117541). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203378. LOC257106 (Accession XM\_170910) is another VGAM559 host target gene. LOC257106 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC257106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257106 BINDING SITE, designated SEQ ID:45679, to the nucleotide sequence of VGAM559 RNA, herein designated VGAM RNA, also designated SEQ ID:3270.

[24397] Another function of VGAM559 is therefore inhibition of

LOC257106 (Accession XM\_170910). Accordingly, utilities of VGAM559 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257106. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 560 (VGAM560) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24398] VGAM560 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM560 was detected is described hereinabove with reference to Figs. 1–8.

[24399] VGAM560 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM560 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24400] VGAM560 gene encodes a VGAM560 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM560 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM560 precursor RNA is designated SEQ ID:546, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:546 is located at position 23914 relative to the genome of Fowlpox Virus.

[24401] VGAM560 precursor RNA folds onto itself, forming VGAM560 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24402] An enzyme complex designated DICER COMPLEX, `dices` the VGAM560 folded precursor RNA into VGAM560 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide se-

quence of VGAM560 RNA is designated SEQ ID:3271, and is provided hereinbelow with reference to the sequence listing part.

[24403] VGAM560 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM560 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM560 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[24404] VGAM560 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM560 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM560 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM560 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM560 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24405] The complementary binding of VGAM560 RNA, herein designated VGAM RNA, to host target binding sites on VGAM560 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM560 host target RNA into VGAM560 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24406] It is appreciated that VGAM560 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM560 host target genes. The mRNA of each one of this plurality of VGAM560 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM560 RNA, herein designated VGAM RNA, and which when bound by VGAM560 RNA causes inhibition of translation of respective one or more VGAM560 host target proteins.

[24407] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM560 gene, herein designated VGAM GENE, on one or more VGAM560 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24408] It is yet further appreciated that a function of VGAM560 is



inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM560 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM560 correlate with, and may be deduced from, the identity of the host target genes which VGAM560 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24409] Nucleotide sequences of the VGAM560 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM560 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM560 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM560 are further described hereinbelow with reference to Table 1.

[24410] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM560 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM560 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24411] As mentioned hereinabove with reference to Fig. 1, a function of VGAM560 gene, herein designated VGAM is inhibition of expression of VGAM560 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM560 correlate with, and may be deduced from, the identity of the target genes which VGAM560 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24412] SB52 (Accession NM\_138335) is a VGAM560 host target gene. SB52 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SB52, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SB52 BINDING SITE, designated SEQ ID:28733, to the nucleotide sequence of VGAM560 RNA, herein designated VGAM RNA, also designated SEQ ID:3271.

[24413] A function of VGAM560 is therefore inhibition of SB52 (Accession NM\_138335). Accordingly, utilities of VGAM560 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SB52. Ubiquitin-like, Containing PHD and RING Finger Domains, 2 (UHRF2, Accession XM\_055929) is another VGAM560

host target gene. UHRF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UHRF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UHRF2 BINDING SITE, designated SEQ ID:36353, to the nucleotide sequence of VGAM560 RNA, herein designated VGAM RNA, also designated SEQ ID:3271.

[24414] Another function of VGAM560 is therefore inhibition of Ubiquitin-like, Containing PHD and RING Finger Domains, 2 (UHRF2, Accession XM\_055929). Accordingly, utilities of VGAM560 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UHRF2. LOC50999 (Accession NM\_016040) is another VGAM560 host target gene. LOC50999 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC50999, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC50999 BINDING SITE, designated SEQ ID:18117, to the nucleotide sequence of VGAM560 RNA, herein designated VGAM RNA,

also designated SEQ ID:3271.

[24415] Another function of VGAM560 is therefore inhibition of LOC50999 (Accession NM\_016040). Accordingly, utilities of VGAM560 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC50999. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 561 (VGAM561) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24416] VGAM561 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM561 was detected is described hereinabove with reference to Figs. 1–8.

[24417] VGAM561 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM561 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24418] VGAM561 gene encodes a VGAM561 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM561 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM561 precursor RNA is designated SEQ ID:547, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:547 is located at position 33749 relative to the genome of Fowlpox Virus.

[24419] VGAM561 precursor RNA folds onto itself, forming VGAM561 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24420] An enzyme complex designated DICER COMPLEX, `dices` the VGAM561 folded precursor RNA into VGAM561 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM561 RNA is designated SEQ ID:3272, and is provided hereinbelow with reference to the sequence listing part.

[24421] VGAM561 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM561 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM561 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[24422] VGAM561 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM561 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM561 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM561 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM561 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24423] The complementary binding of VGAM561 RNA, herein designated VGAM RNA, to host target binding sites on VGAM561 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM561 host target RNA into VGAM561 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24424] It is appreciated that VGAM561 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM561 host target genes. The mRNA of

each one of this plurality of VGAM561 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM561 RNA, herein designated VGAM RNA, and which when bound by VGAM561 RNA causes inhibition of translation of respective one or more VGAM561 host target proteins.

[24425] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM561 gene, herein designated VGAM GENE, on one or more VGAM561 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science



294,779 (2001)).

[24426] It is yet further appreciated that a function of VGAM561 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM561 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM561 correlate with, and may be deduced from, the identity of the host target genes which VGAM561 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24427] Nucleotide sequences of the VGAM561 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM561 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM561 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM561 are further described hereinbelow with reference to Table 1.

[24428] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM561 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM561 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[24429] As mentioned hereinabove with reference to Fig. 1, a function of VGAM561 gene, herein designated VGAM is inhibition of expression of VGAM561 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM561 correlate with, and may be deduced from, the identity of the target genes which VGAM561 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24430] BLAME (Accession NM\_020125) is a VGAM561 host target gene. BLAME BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BLAME, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLAME BINDING SITE, designated SEQ ID:21305, to the nucleotide sequence of VGAM561 RNA, herein designated VGAM RNA, also designated SEQ ID:3272.

[24431] A function of VGAM561 is therefore inhibition of BLAME (Accession NM\_020125). Accordingly, utilities of VGAM561 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with BLAME. LOC90342 (Accession XM\_031009) is another VGAM561 host target gene. LOC90342 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90342, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90342 BINDING SITE, designated SEQ ID:31252, to the nucleotide sequence of VGAM561 RNA, herein designated VGAM RNA, also designated SEQ ID:3272.

[24432] Another function of VGAM561 is therefore inhibition of LOC90342 (Accession XM\_031009). Accordingly, utilities of VGAM561 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90342. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 562 (VGAM562) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24433] VGAM562 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM562 was detected is described hereinabove with reference to Figs. 1–8.

[24434] VGAM562 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM562 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24435] VGAM562 gene encodes a VGAM562 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM562 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM562 precursor RNA is designated SEQ ID:548, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:548 is located at position 81779 relative to the genome of Fowlpox Virus.

[24436] VGAM562 precursor RNA folds onto itself, forming VGAM562 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24437] An enzyme complex designated DICER COMPLEX, `dices` the VGAM562 folded precursor RNA into VGAM562 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 56%) nucleotide sequence of VGAM562 RNA is designated SEQ ID:3273, and is provided hereinbelow with reference to the sequence listing part.

[24438] VGAM562 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM562 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM562 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24439] VGAM562 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM562 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM562 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM562 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM562 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24440] The complementary binding of VGAM562 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM562 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM562 host target RNA into VGAM562 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24441] It is appreciated that VGAM562 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM562 host target genes. The mRNA of each one of this plurality of VGAM562 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM562 RNA, herein designated VGAM RNA, and which when bound by VGAM562 RNA causes inhibition of translation of respective one or more VGAM562 host target proteins.

[24442] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM562 gene, herein designated VGAM GENE, on one or more VGAM562 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24443] It is yet further appreciated that a function of VGAM562 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM562 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM562 correlate with, and may be deduced from, the identity of the host target genes which VGAM562 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24444] Nucleotide sequences of the VGAM562 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the



`diced` VGAM562 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM562 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM562 are further described hereinbelow with reference to Table 1.

[24445] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM562 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM562 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24446] As mentioned hereinabove with reference to Fig. 1, a function of VGAM562 gene, herein designated VGAM is inhibition of expression of VGAM562 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM562 correlate with, and may be deduced from, the identity of the target genes which VGAM562 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24447] BCRP2 (Accession XM\_031102) is a VGAM562 host target gene. BCRP2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by

BCRP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCRP2 BINDING SITE, designated SEQ ID:31278, to the nucleotide sequence of VGAM562 RNA, herein designated VGAM RNA, also designated SEQ ID:3273.

[24448] A function of VGAM562 is therefore inhibition of BCRP2 (Accession XM\_031102). Accordingly, utilities of VGAM562 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCRP2. Forkhead Box O1A (rhabdomyosarcoma) (FOXO1A, Accession NM\_002015) is another VGAM562 host target gene. FOXO1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FOXO1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOXO1A BINDING SITE, designated SEQ ID:7757, to the nucleotide sequence of VGAM562 RNA, herein designated VGAM RNA, also designated SEQ ID:3273.

[24449] Another function of VGAM562 is therefore inhibition of

Forkhead Box O1A (rhabdomyosarcoma) (FOXO1A, Accession NM\_002015), a gene which is a probable transcription factor. Accordingly, utilities of VGAM562 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOXO1A. The function of FOXO1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM228. Interleukin 20 Receptor, Alpha (IL20RA, Accession NM\_014432) is another VGAM562 host target gene. IL20RA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL20RA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL20RA BINDING SITE, designated SEQ ID:15789, to the nucleotide sequence of VGAM562 RNA, herein designated VGAM RNA, also designated SEQ ID:3273.

[24450] Another function of VGAM562 is therefore inhibition of Interleukin 20 Receptor, Alpha (IL20RA, Accession NM\_014432), a gene which is the receptor for interleukin-20 . Accordingly, utilities of VGAM562 include diagnosis,

prevention and treatment of diseases and clinical conditions associated with IL20RA. The function of IL20RA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM315. TACTILE (Accession NM\_005816) is another VGAM562 host target gene. TACTILE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TACTILE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TACTILE BINDING SITE, designated SEQ ID:12408, to the nucleotide sequence of VGAM562 RNA, herein designated VGAM RNA, also designated SEQ ID:3273.

[24451] Another function of VGAM562 is therefore inhibition of TACTILE (Accession NM\_005816). Accordingly, utilities of VGAM562 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TACTILE. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 563 (VGAM563) viral gene, which modulates expression of

respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24452] VGAM563 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM563 was detected is described hereinabove with reference to Figs. 1–8.

[24453] VGAM563 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM563 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24454] VGAM563 gene encodes a VGAM563 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM563 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM563 precursor RNA is designated SEQ ID:549, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:549 is located at position 82125 relative to the genome of Fowlpox Virus.

[24455] VGAM563 precursor RNA folds onto itself, forming VGAM563 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[24456] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM563 folded precursor RNA into VGAM563 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 56%) nucleotide se-  
quence of VGAM563 RNA is designated SEQ ID:3274, and  
is provided hereinbelow with reference to the sequence  
listing part.

[24457] VGAM563 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM563 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM563 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24458] VGAM563 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM563 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM563 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM563 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM563 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24459] The complementary binding of VGAM563 RNA, herein designated VGAM RNA, to host target binding sites on VGAM563 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM563 host target RNA into VGAM563 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24460] It is appreciated that VGAM563 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM563 host target genes. The mRNA of each one of this plurality of VGAM563 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM563 RNA, herein designated VGAM RNA, and which when bound by VGAM563 RNA causes inhibition of translation of respective one or more VGAM563 host target proteins.

[24461] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by



VGAM563 gene, herein designated VGAM GENE, on one or more VGAM563 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24462] It is yet further appreciated that a function of VGAM563 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM563 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM563 correlate with, and may be deduced from, the identity of the host target genes which VGAM563 binds and inhibits, and the function of these host target genes, as elaborated herein—

below.

- [24463] Nucleotide sequences of the VGAM563 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM563 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM563 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM563 are further described hereinbelow with reference to Table 1.
- [24464] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM563 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM563 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [24465] As mentioned hereinabove with reference to Fig. 1, a function of VGAM563 gene, herein designated VGAM is inhibition of expression of VGAM563 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM563 correlate with, and may be deduced from, the identity of the target genes which VGAM563 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24466] Nuclear Receptor Subfamily 2, Group F, Member 2 (NR2F2, Accession NM\_021005) is a VGAM563 host target gene. NR2F2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NR2F2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR2F2 BINDING SITE, designated SEQ ID:22001, to the nucleotide sequence of VGAM563 RNA, herein designated VGAM RNA, also designated SEQ ID:3274.

[24467] A function of VGAM563 is therefore inhibition of Nuclear Receptor Subfamily 2, Group F, Member 2 (NR2F2, Accession NM\_021005), a gene which is the regulation of the apolipoprotein ai gene transcription. Accordingly, utilities of VGAM563 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR2F2. The function of NR2F2 has been established by previous studies. Hepatocyte-specific expression of the human apolipoprotein A-I gene (OMIM Ref. No. 107680) is dependent on synergistic actions between nuclear proteins bound to distinct sites within a liver-specific enhancer located upstream of the APOA1 transcription start site

(Widom et al., 1991). From analysis of the cDNA-derived amino acid sequence, Ladas and Karathanasis (1991) found that one of these proteins, apolipoprotein regulatory protein I, is a novel member of the steroid/thyroid nuclear receptor of ligand-dependent transcription factors. Using a 3.9-kb fragment, Modi et al. (1991) assigned the NR2F2 gene to 15q26.1–q26.2 by Southern analysis of human–rodent somatic cell hybrid DNAs and in situ chromosomal hybridization. Chicken ovalbumin upstream promoter transcription factors (COUP-TFs) are members of the steroid/thyroid hormone receptor superfamily. They are often called orphan receptors, since their ligands have not been identified. COUP-TF homologs have been cloned in many species, from *Drosophila* to human. The protein sequences are highly homologous across species, suggesting functional conservation. ARP1, also called COUP-TFII, and COUP-TFI (OMIM Ref. No. 132890), were cloned from the human and their genomic organization characterized. Qiu et al. (1995) isolated the mouse genes encoding COUP-TFs I and II and characterized their genomic structures. Both have relatively simple structures similar to those of their human counterparts. Qiu et al. (1995) used interspecific backcross analysis to map *Tcfcoup1* to

mouse chromosome 13 and Tcf coup2 to mouse chromosome 7. By isotopic in situ hybridization, they mapped the human counterparts to 5q14 and 15q26, in regions that show homology of synteny between mouse and human. The previous assignment of the so-called ARP1 gene was confirmed.

- [24468] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [24469] Qiu, Y.; Krishnan, V.; Zeng, Z.; Gilbert, D. J.; Copeland, N. G.; Gibson, L.; Yang-Feng, T.; Jenkins, N. A.; Tsai, M.-J.; Tsai, S. Y. : Isolation, characterization, and chromosomal localization of mouse and human COUP-TF I and II genes. Genomics 29: 240–246, 1995. ; and
- [24470] Widom, R. L.; Ladias, J. A. A.; Kouidou, S.; Karathanasis, S. K. : Synergistic interactions between transcription factors control expression of the apolipoprotein AI gene in liver cells.
- [24471] Further studies establishing the function and utilities of NR2F2 are found in John Hopkins OMIM database record ID 107773, and in cited publications numbered 12069, 12071–12072, 402 and 12073 listed in the bibliography section hereinbelow, which are also hereby incorporated

by reference. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 564 (VGAM564) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24472] VGAM564 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM564 was detected is described hereinabove with reference to Figs. 1–8.

[24473] VGAM564 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM564 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24474] VGAM564 gene encodes a VGAM564 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM564 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM564 precursor RNA is designated SEQ ID:550, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:550 is located at position 81158 relative to the genome of Fowlpox Virus.

[24475] VGAM564 precursor RNA folds onto itself, forming VGAM564 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

‘hairpin structure’, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[24476] An enzyme complex designated DICER COMPLEX, ‘dices’ the VGAM564 folded precursor RNA into VGAM564 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, ‘dicing’ of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 53%) nucleotide sequence of VGAM564 RNA is designated SEQ ID:3275, and is provided hereinbelow with reference to the sequence listing part.

[24477] VGAM564 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM564 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM564 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5’ untranslated region, a protein coding region and a 3’ untranslated region, designated 5’UTR, PROTEIN



CODING and 3`UTR respectively.

[24478] VGAM564 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM564 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM564 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM564 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM564 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24479] The complementary binding of VGAM564 RNA, herein designated VGAM RNA, to host target binding sites on VGAM564 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM564 host target RNA into VGAM564 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24480] It is appreciated that VGAM564 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM564 host target genes. The mRNA of each one of this plurality of VGAM564 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM564 RNA, herein designated VGAM RNA, and which when bound by VGAM564 RNA causes inhibition of translation of respective one or more VGAM564 host target proteins.

[24481] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM564 gene, herein designated VGAM GENE, on one or more VGAM564 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24482] It is yet further appreciated that a function of VGAM564 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM564 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM564 correlate with, and may be deduced from, the identity of the host target genes which VGAM564 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24483] Nucleotide sequences of the VGAM564 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM564 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM564 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM564 are further  
described hereinbelow with reference to Table 1.

[24484] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM564 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM564 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[24485] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM564 gene, herein designated VGAM is  
inhibition of expression of VGAM564 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM564 correlate with, and may be deduced  
from, the identity of the target genes which VGAM564  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[24486] Deducator of Cyto-kinesis 1 (DOCK1, Accession  
NM\_001380) is a VGAM564 host target gene. DOCK1

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DOCK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DOCK1 BINDING SITE, designated SEQ ID:7050, to the nucleotide sequence of VGAM564 RNA, herein designated VGAM RNA, also designated SEQ ID:3275.

[24487] A function of VGAM564 is therefore inhibition of Dedicator of Cytokinesis 1 (DOCK1, Accession NM\_001380), a gene which may function in the extension of cell surfaces. Accordingly, utilities of VGAM564 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DOCK1. The function of DOCK1 has been established by previous studies. The CRK protein (OMIM Ref. No. 164762), comprised mostly of SH2 and SH3 src-homology domains, has an important role in signaling from focal adhesions. Along with other adaptor proteins such as GRB2 (OMIM Ref. No. 108355) and NCK (OMIM Ref. No. 600508), it receives signals through its SH2 domains from phosphotyrosine-containing peptides and transfers them to other proteins bound to its SH3 domains. Among proteins that bind to the SH3 domain of

CRK are C3G (OMIM Ref. No. 600303), a guanine nucleotide exchange protein for RAP1 (OMIM Ref. No. 600278), and the 180-kD DOCK (downstream of CRK) protein. Hasegawa et al. (1996) isolated a cDNA for DOCK by screening an expression library with CRK SH3. They found a full-length cDNA that encodes a putative 1,866-amino acid polypeptide with an SH3 domain at its amino end. Northern blots showed a 7.6-kb transcript that was expressed in most tissues and most strongly in placenta, lungs, kidney, and pancreas. Wildtype DOCK180 was found in the cytoplasm and did not affect cell morphology. However, when farnesylated, the protein became associated with the cytoplasmic membrane and made spindle 3T3 cells become flattened and polygonal. Takai et al. (1996) mapped DOCK180 to 10q26.13-q26.3 by fluorescence in situ hybridization. During programmed cell death (apoptosis), cell corpses are rapidly engulfed. This engulfment process involves the recognition and subsequent phagocytosis of cell corpses by engulfing cells. Wu and Horvitz (1998) shed light on the previously obscure mechanisms by which cell corpses are engulfed. They reported that *ced-5*, a gene that is required for cell-corpse engulfment in the nematode *Caenorhabditis ele-*

gans, encodes a protein that is similar to the human protein DOCK180 and the *Drosophila melanogaster* protein Myoblast City (MBC), both of which had been implicated in the extension of cell surfaces. *C. elegans* ced-5 mutants were defective not only in the engulfment of cell corpses but also in the migrations of 2 specific gonadal cells, the distal tip cells. The expression of human DOCK180 in *C. elegans* rescued the cell-migration defect of a ced-5 mutant. Wu and Horvitz (1998) presented evidence that ced-5 functions in engulfing cells during the engulfment of cell corpses. They suggested that ced-5 acts in the extension of the surface of an engulfing cell around a dying cell during programmed cell death. They named the new family of proteins that function in the extension of cell surfaces the CDM (for CED-5, DOCK180, and MBC) family.

[24488] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24489] Savill, J. : Phagocytic docking without shocking. *Nature* 442-443, 1998. ; and

[24490] Takai, S.; Hasegawa, H.; Kiyokawa, E.; Yamada, K.; Kurata, T.; Matsuda, M. : Chromosomal mapping of the gene encoding DOCK180, a major Crk-binding protein, to

10q26.13–q26.3 by fluoresc.

[24491] Further studies establishing the function and utilities of DOCK1 are found in John Hopkins OMIM database record ID 601403, and in cited publications numbered 6497–6500 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC146452 (Accession XM\_085473) is another VGAM564 host target gene. LOC146452 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146452 BINDING SITE, designated SEQ ID:38162, to the nucleotide sequence of VGAM564 RNA, herein designated VGAM RNA, also designated SEQ ID:3275.

[24492] Another function of VGAM564 is therefore inhibition of LOC146452 (Accession XM\_085473). Accordingly, utilities of VGAM564 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146452. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-



dress Messenger 565 (VGAM565) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24493] VGAM565 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM565 was detected is described hereinabove with reference to Figs. 1–8.

[24494] VGAM565 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM565 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24495] VGAM565 gene encodes a VGAM565 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM565 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM565 precursor RNA is designated SEQ ID:551, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:551 is located at position 104297 relative to the genome of Fowlpox Virus.

[24496] VGAM565 precursor RNA folds onto itself, forming VGAM565 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24497] An enzyme complex designated DICER COMPLEX, `dices` the VGAM565 folded precursor RNA into VGAM565 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM565 RNA is designated SEQ ID:3276, and is provided hereinbelow with reference to the sequence listing part.

[24498] VGAM565 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM565 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM565 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24499] VGAM565 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM565 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM565 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM565 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM565 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24500] The complementary binding of VGAM565 RNA, herein designated VGAM RNA, to host target binding sites on VGAM565 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM565 host target RNA into VGAM565 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24501] It is appreciated that VGAM565 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM565 host target genes. The mRNA of each one of this plurality of VGAM565 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM565 RNA, herein designated VGAM RNA, and which when bound by VGAM565 RNA causes inhibition of translation of respective one or more VGAM565 host target proteins.

[24502] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM565 gene, herein designated VGAM GENE, on one or more VGAM565 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24503] It is yet further appreciated that a function of VGAM565 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM565 correlate with, and may be deduced from, the identity of the host

target genes which VGAM565 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24504] Nucleotide sequences of the VGAM565 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM565 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM565 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM565 are further described hereinbelow with reference to Table 1.

[24505] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM565 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM565 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24506] As mentioned hereinabove with reference to Fig. 1, a function of VGAM565 gene, herein designated VGAM is inhibition of expression of VGAM565 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM565 correlate with, and may be deduced from, the identity of the target genes which VGAM565

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24507] Aldehyde Dehydrogenase 1 Family, Member A3

(ALDH1A3, Accession NM\_000693) is a VGAM565 host target gene. ALDH1A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALDH1A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALDH1A3 BINDING SITE, designated SEQ ID:6352, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24508] A function of VGAM565 is therefore inhibition of Aldehyde Dehydrogenase 1 Family, Member A3 (ALDH1A3, Accession NM\_000693), a gene which plays a major role in the detoxification of aldehydes generated by alcohol metabolism and lipid peroxidation. Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALDH1A3. The function of ALDH1A3 has been established by previous studies. Hsu et al. (1994) identified and characterized the ALDH6 gene. The existence of this unique

ALDH isozyme in human saliva and its polymorphism had previously been demonstrated. The ALDH6 cDNA is 3,457 bp long and contains an open reading frame encoding 512 amino acids. The deduced amino acid sequence shows that the protein is larger than human liver ALDH1 (OMIM Ref. No. 100640) by 11 residues at the N terminus, and the degree of identity between the 2 isozymes is 70% with an alignment of 500 amino acid residues. Northern blot analysis demonstrated that the ALDH6 gene is expressed at low levels in many tissues and at higher levels in salivary gland, stomach, and kidney. By in situ hybridization of chick and mouse embryos, Grun et al. (2000) demonstrated expression of Aldh1a3 in the developing sensory neuroepithelia of the eye, nose, and ear, and in discrete sites within the central nervous system. Expression of chick Aldh1a3 in a human choriocarcinoma cell line conferred increased sensitivity to retinol in a retinoic acid receptor (see OMIM Ref. No. 180240)-dependent reporter assay. GENE STRUCTURE Hsu et al. (1994) determined that the ALDH6 gene spans about 37 kb and contains 13 exons. Putative TATA and CCAAT boxes and Sp1 binding sites were found in the 5-prime upstream region of the gene.



- [24509] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [24510] Grun, F.; Hirose, Y.; Kawauchi, S.; Ogura, T.; Umesono, K. : Aldehyde dehydrogenase 6, a cytosolic retinaldehyde dehydrogenase prominently expressed in sensory neuroepithelia during development. J. Biol. Chem. 275: 41210–41218, 2000. ; and
- [24511] Hsu, L. C.; Chang, W.-C.; Hiraoka, L.; Hsieh, C.-L. : Molecular cloning, genomic organization, and chromosomal localization of an additional human aldehyde dehydrogenase gene, ALDH6. G.
- [24512] Further studies establishing the function and utilities of ALDH1A3 are found in John Hopkins OMIM database record ID 600463, and in cited publications numbered 1613–1614 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Glial Fibrillary Acidic Protein (GFAP, Accession NM\_002055) is another VGAM565 host target gene. GFAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GFAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of GFAP BINDING SITE, designated SEQ ID:7816, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24513] Another function of VGAM565 is therefore inhibition of Glial Fibrillary Acidic Protein (GFAP, Accession NM\_002055). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GFAP. Protein Phosphatase 2, Regulatory Subunit B (B56), Epsilon Isoform (PPP2R5E, Accession NM\_006246) is another VGAM565 host target gene. PPP2R5E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2R5E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R5E BINDING SITE, designated SEQ ID:12920, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24514] Another function of VGAM565 is therefore inhibition of Protein Phosphatase 2, Regulatory Subunit B (B56), Epsilon Isoform (PPP2R5E, Accession NM\_006246), a gene which

is a regulatory subunit of protein phosphatase 2A. Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R5E. The function of PPP2R5E and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM302. Prolactin Regulatory Element Binding (PREB, Accession NM\_013388) is another VGAM565 host target gene. PREB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PREB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PREB BINDING SITE, designated SEQ ID:15038, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24515] Another function of VGAM565 is therefore inhibition of Prolactin Regulatory Element Binding (PREB, Accession NM\_013388), a gene which is a WD motif DNA-binding protein and involved in transcriptional regulation. Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with PREB. The function of PREB has been established by previous studies. Fliss et al. (1999) isolated a rat cDNA encoding Preb, a WD motif DNA-binding protein with the capacity to regulate prolactin (PRL; 176760) promoter activity. Northern blot analysis of human tissues using a rat Preb cDNA probe showed expression of a 2.2-kb transcript in heart, brain, placenta, liver, skeletal muscle, kidney, and pancreas; a 1.9-kb transcript in brain, placenta, and lung; and a 1.5-kb transcript heart, skeletal muscle, and pancreas. By screening a fetal brain cDNA library with a rat Preb probe, followed by 5-prime primer walking, Taylor Clelland et al. (2000) isolated a cDNA encoding human PREB. The deduced 417-amino acid protein, which is 89% identical to the rat protein, has 3 conserved WD repeats and 2 conserved pro-gln-rich regions. RNA dot blot analysis detected variable expression of PREB in all adult and fetal tissues. They proposed that PREB is a DNA-binding factor during mammalian development and that abnormal dosage may play a role in some of the phenotypic abnormalities observed in the partial trisomy 2p syndrome, which is characterized by a number of congenital defects, including genital abnormalities.

[24516] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [24517] Fliss, M. S.; Hinkle, P. M.; Bancroft, C. : Expression cloning and characterization of PREB (prolactin regulatory element binding), a novel WD motif DNA-binding protein with a capacity to regulate prolactin promoter activity. *Molec. Endocr.* 13: 644–657, 1999. ; and
- [24518] Taylor Clelland, C. L.; Levy, B.; McKie, J. M.; Duncan, A. M. V.; Hirschhorn, K.; Bancroft, C. : Cloning and characterization of human PREB; a gene that maps to a genomic region associ.
- [24519] Further studies establishing the function and utilities of PREB are found in John Hopkins OMIM database record ID 606395, and in cited publications numbered 6795–6796 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger Protein 24 (K0X 17) (ZNF24, Accession NM\_006965) is another VGAM565 host target gene. ZNF24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF24 BINDING SITE,

designated SEQ ID:13838, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24520] Another function of VGAM565 is therefore inhibition of Zinc Finger Protein 24 (KOX 17) (ZNF24, Accession NM\_006965). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF24. FLJ22028 (Accession NM\_024854) is another VGAM565 host target gene. FLJ22028 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22028 BINDING SITE, designated SEQ ID:24286, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24521] Another function of VGAM565 is therefore inhibition of FLJ22028 (Accession NM\_024854). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22028. KIAA0626 (Accession NM\_021647) is another VGAM565

host target gene. KIAA0626 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0626, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0626 BINDING SITE, designated SEQ ID:22315, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24522] Another function of VGAM565 is therefore inhibition of KIAA0626 (Accession NM\_021647). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0626. KIAA0794 (Accession XM\_087353) is another VGAM565 host target gene. KIAA0794 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0794, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0794 BINDING SITE, designated SEQ ID:39184, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24523] Another function of VGAM565 is therefore inhibition of KIAA0794 (Accession XM\_087353). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0794. LOC157421 (Accession XM\_098756) is another VGAM565 host target gene. LOC157421 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC157421, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157421 BINDING SITE, designated SEQ ID:41793, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24524] Another function of VGAM565 is therefore inhibition of LOC157421 (Accession XM\_098756). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157421. LOC257048 (Accession XM\_171240) is another VGAM565 host target gene. LOC257048 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC257048, corresponding to a HOST TARGET binding site such as BIND-



ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257048 BINDING SITE, designated SEQ ID:46027, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24525] Another function of VGAM565 is therefore inhibition of LOC257048 (Accession XM\_171240). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257048. LOC84549 (Accession NM\_032509) is another VGAM565 host target gene. LOC84549 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC84549, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC84549 BINDING SITE, designated SEQ ID:26255, to the nucleotide sequence of VGAM565 RNA, herein designated VGAM RNA, also designated SEQ ID:3276.

[24526] Another function of VGAM565 is therefore inhibition of LOC84549 (Accession NM\_032509). Accordingly, utilities of VGAM565 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC84549. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 566 (VGAM566) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24527] VGAM566 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM566 was detected is described hereinabove with reference to Figs. 1–8.

[24528] VGAM566 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM566 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24529] VGAM566 gene encodes a VGAM566 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM566 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM566 precursor RNA is designated SEQ ID:552, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:552 is located at position 101053 relative to the genome of Fowlpox Virus.

[24530] VGAM566 precursor RNA folds onto itself, forming VGAM566 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24531] An enzyme complex designated DICER COMPLEX, `dices` the VGAM566 folded precursor RNA into VGAM566 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM566 RNA is designated SEQ ID:3277, and is provided hereinbelow with reference to the sequence listing part.

[24532] VGAM566 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM566 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM566 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24533] VGAM566 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM566 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM566 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM566 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM566 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24534] The complementary binding of VGAM566 RNA, herein designated VGAM RNA, to host target binding sites on VGAM566 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM566 host target RNA into VGAM566 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24535] It is appreciated that VGAM566 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM566 host target genes. The mRNA of each one of this plurality of VGAM566 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM566 RNA, herein designated VGAM RNA, and which when bound by VGAM566 RNA causes in-

hibition of translation of respective one or more VGAM566 host target proteins.

[24536] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM566 gene, herein designated VGAM GENE, on one or more VGAM566 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24537] It is yet further appreciated that a function of VGAM566 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM566 include diagnosis, prevention and

treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM566 correlate with, and may be deduced from, the identity of the host target genes which VGAM566 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [24538] Nucleotide sequences of the VGAM566 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM566 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM566 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM566 are further described hereinbelow with reference to Table 1.
- [24539] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM566 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM566 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [24540] As mentioned hereinabove with reference to Fig. 1, a function of VGAM566 gene, herein designated VGAM is inhibition of expression of VGAM566 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM566 correlate with, and may be deduced from, the identity of the target genes which VGAM566 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24541] Cytochrome P450, 51 (lanosterol 14- $\alpha$ -demethylase) (CYP51, Accession NM\_000786) is a VGAM566 host target gene. CYP51 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP51, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP51 BINDING SITE, designated SEQ ID:6435, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24542] A function of VGAM566 is therefore inhibition of Cytochrome P450, 51 (lanosterol 14- $\alpha$ -demethylase) (CYP51, Accession NM\_000786). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP51. Mannan-binding Lectin Serine Protease 1 (C4/C2 activating component of Ra-reactive factor) (MASP1, Accession



NM\_139125) is another VGAM566 host target gene.

MASP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MASP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MASP1 BINDING SITE, designated SEQ ID:29157, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24543] Another function of VGAM566 is therefore inhibition of Mannan-binding Lectin Serine Protease 1 (C4/C2 activating component of Ra-reactive factor) (MASP1, Accession NM\_139125), a gene which a complement-dependent bactericidal factor. Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MASP1. The function of MASP1 has been established by previous studies. The Ra-reactive factor (RARF) is a complement-dependent bactericidal factor that binds to the Ra and R2 polysaccharides expressed by certain enterobacteria. RARF activity is found in the sera of a diverse group of vertebrates, suggesting that it is an evolutionarily conserved mechanism

to resist infection by these bacterial strains. RARF includes a 100-kD component, CRARF, also called MASP1 or p100, that was thought to activate the complement components C4 (C4F, 120820; C4S, 120810), C2 (OMIM Ref. No. 217000), and C3 (OMIM Ref. No. 120700). Subsequent work, however, separated MASP1 from MASP2 (OMIM Ref. No. 605102) and showed that MASP1 activates C3 and C2, whereas MASP2 activates C4 and C2. The other component of RARF is mannan-binding lectin (OMIM Ref. No. 154545), a plasma protein member of the complement system that binds to microbial carbohydrates and activates the MASPs. The MASPs then recruit C4 and C2 to generate the C3 convertase or directly activate C3. Takada et al. (1993) cloned a partial human CRARF cDNA from a liver library. The human CRARF amino acid sequence is similar to the human complement subcomponents C1R (OMIM Ref. No. 216950) and C1S (OMIM Ref. No. 120580). Takada et al. (1995) obtained a corresponding mouse cDNA. By RT-PCR with primers based on N-terminal peptide sequence analysis and the consensus sequence of serine proteases, followed by screening a fetal liver cDNA library, Sato et al. (1994) isolated a cDNA encoding MASP. Sequence analysis predicted that the 699-amino acid pro-

tein contains a leader peptide; 2 structural domains similar to those of C1R and C1S; an EGF-like domain thought to be related to calcium-binding activity; 2 short consensus repeat domains; and a serine protease domain. Northern blot analysis revealed expression of 4.8- and 3.4-kb MASP transcripts in fetal liver; no expression was detected in adult tissues or in fetal heart, brain, lung, or kidney.

Sato et al. (1994) proposed that the MBL-MASP complex is a novel activator of complement in what they designated the lectin pathway. By biochemical purification of plasma proteins and immunoblot analysis, Dahl et al. (2001) detected a 42-kD serine protease associated with MBL. They identified a cDNA encoding this protein, MASP3, which is generated by alternative splicing of MASP1. The MASP3 transcription product is composed of an A chain, which is common to both MASP1 and MASP3, and a B chain, which is unique to MASP3. The deduced 728-amino acid MASP3 protein has a signal peptide, 3 N-glycosylation sites on the B chain and 4 on the A chain. Sato et al. (1994) mapped the MASP1 gene to 3q27-q28 by FISH. Using FISH, Takada et al. (1995) mapped the human CRARF gene to 3q27-q28 and the mouse gene to 16B2-B3, regions thought to share homology of synteny.

[24544] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24545] Dahl, M. R.; Thiel, S.; Matsushita, M.; Fujita, T.; Willis, A. C.; Christensen, T.; Vorup-Jensen, T.; Jensenius, J. C. : MASP-3 and its association with distinct complexes of the mannan-binding lectin complement activation pathway. *Immunity* 15: 127-135, 2001. ; and

[24546] Takada, F.; Seki, N.; Matsuda, Y.; Takayama, Y.; Kawakami, M. : Localization of the genes for the 100-kDa complement-activating components of Ra-reactive factor (CRARF and Crarf) to hum.

[24547] Further studies establishing the function and utilities of MASP1 are found in John Hopkins OMIM database record ID 600521, and in cited publications numbered 7504-7510 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Kinase, Lysine Deficient 3 (PRKWINK3, Accession XM\_029183) is another VGAM566 host target gene. PRKWINK3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKWINK3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-

ble 2 illustrates the complementarity of the nucleotide sequences of PRKWNK3 BINDING SITE, designated SEQ ID:30854, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24548] Another function of VGAM566 is therefore inhibition of Protein Kinase, Lysine Deficient 3 (PRKWNK3, Accession XM\_029183). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKWNK3. FLJ10199 (Accession XM\_048840) is another VGAM566 host target gene. FLJ10199 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10199, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10199 BINDING SITE, designated SEQ ID:35284, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24549] Another function of VGAM566 is therefore inhibition of FLJ10199 (Accession XM\_048840). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ10199. KIAA0981 (Accession XM\_028867) is another VGAM566 host target gene. KIAA0981 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0981, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0981 BINDING SITE, designated SEQ ID:30794, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24550] Another function of VGAM566 is therefore inhibition of KIAA0981 (Accession XM\_028867). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0981. MGC4832 (Accession NM\_145061) is another VGAM566 host target gene. MGC4832 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4832, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4832 BINDING SITE, designated SEQ ID:29697, to the nucleotide

sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24551] Another function of VGAM566 is therefore inhibition of MGC4832 (Accession NM\_145061). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4832. Ubiquitin-conjugating Enzyme E2D 1 (UBC4/5 homolog, yeast) (UBE2D1, Accession NM\_003338) is another VGAM566 host target gene. UBE2D1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2D1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2D1 BINDING SITE, designated SEQ ID:9345, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24552] Another function of VGAM566 is therefore inhibition of Ubiquitin-conjugating Enzyme E2D 1 (UBC4/5 homolog, yeast) (UBE2D1, Accession NM\_003338). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2D1. ZFP106 (Accession NM\_022473) is another

VGAM566 host target gene. ZFP106 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZFP106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFP106 BINDING SITE, designated SEQ ID:22828, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24553] Another function of VGAM566 is therefore inhibition of ZFP106 (Accession NM\_022473). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFP106. LOC145739 (Accession XM\_085222) is another VGAM566 host target gene. LOC145739 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145739, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145739 BINDING SITE, designated SEQ ID:37966, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.



[24554] Another function of VGAM566 is therefore inhibition of LOC145739 (Accession XM\_085222). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145739. LOC147990 (Accession XM\_097358) is another VGAM566 host target gene. LOC147990 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147990, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147990 BINDING SITE, designated SEQ ID:40862, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24555] Another function of VGAM566 is therefore inhibition of LOC147990 (Accession XM\_097358). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147990. LOC162239 (Accession XM\_091439) is another VGAM566 host target gene. LOC162239 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC162239, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162239 BINDING SITE, designated SEQ ID:40049, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24556] Another function of VGAM566 is therefore inhibition of LOC162239 (Accession XM\_091439). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162239. LOC221395 (Accession XM\_166354) is another VGAM566 host target gene. LOC221395 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221395, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221395 BINDING SITE, designated SEQ ID:44182, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24557] Another function of VGAM566 is therefore inhibition of LOC221395 (Accession XM\_166354). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC221395. LOC254778 (Accession XM\_171193) is another VGAM566 host target gene. LOC254778 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254778, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254778 BINDING SITE, designated SEQ ID:45975, to the nucleotide sequence of VGAM566 RNA, herein designated VGAM RNA, also designated SEQ ID:3277.

[24558] Another function of VGAM566 is therefore inhibition of LOC254778 (Accession XM\_171193). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254778. LOC51026 (Accession NM\_016072) is another VGAM566 host target gene. LOC51026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51026 BINDING SITE, designated SEQ ID:18139, to the nucleotide sequence of VGAM566 RNA, herein designated

VGAM RNA, also designated SEQ ID:3277.

[24559] Another function of VGAM566 is therefore inhibition of LOC51026 (Accession NM\_016072). Accordingly, utilities of VGAM566 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51026. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 567 (VGAM567) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24560] VGAM567 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM567 was detected is described hereinabove with reference to Figs. 1–8.

[24561] VGAM567 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM567 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24562] VGAM567 gene encodes a VGAM567 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM567 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM567 precursor RNA is designated SEQ ID:553, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:553 is located at position 126386 relative to the genome of Fowlpox Virus.

[24563] VGAM567 precursor RNA folds onto itself, forming VGAM567 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24564] An enzyme complex designated DICER COMPLEX, `dices` the VGAM567 folded precursor RNA into VGAM567 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 77%) nucleotide sequence of VGAM567 RNA is designated SEQ ID:3278, and is provided hereinbelow with reference to the sequence listing part.

[24565] VGAM567 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM567 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM567 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24566] VGAM567 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM567 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM567 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM567 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM567 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24567] The complementary binding of VGAM567 RNA, herein designated VGAM RNA, to host target binding sites on VGAM567 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM567 host target RNA into VGAM567 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24568] It is appreciated that VGAM567 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM567 host target genes. The mRNA of

each one of this plurality of VGAM567 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM567 RNA, herein designated VGAM RNA, and which when bound by VGAM567 RNA causes inhibition of translation of respective one or more VGAM567 host target proteins.

[24569] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM567 gene, herein designated VGAM GENE, on one or more VGAM567 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science



294,779 (2001)).

[24570] It is yet further appreciated that a function of VGAM567 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM567 correlate with, and may be deduced from, the identity of the host target genes which VGAM567 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24571] Nucleotide sequences of the VGAM567 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM567 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM567 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM567 are further described hereinbelow with reference to Table 1.

[24572] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM567 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM567 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[24573] As mentioned hereinabove with reference to Fig. 1, a function of VGAM567 gene, herein designated VGAM is inhibition of expression of VGAM567 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM567 correlate with, and may be deduced from, the identity of the target genes which VGAM567 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24574] ATPase, Na<sup>+</sup>/K<sup>+</sup> Transporting, Alpha 2 (+) Polypeptide (ATP1A2, Accession NM\_000702) is a VGAM567 host target gene. ATP1A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP1A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP1A2 BINDING SITE, designated SEQ ID:6372, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24575] A function of VGAM567 is therefore inhibition of ATPase, Na<sup>+</sup>/K<sup>+</sup> Transporting, Alpha 2 (+) Polypeptide (ATP1A2,

Accession NM\_000702). Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP1A2. Wolf-Hirschhorn Syndrome Candidate 1 (WHSC1, Accession NM\_007331) is another VGAM567 host target gene. WHSC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WHSC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WHSC1 BINDING SITE, designated SEQ ID:14252, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24576] Another function of VGAM567 is therefore inhibition of Wolf-Hirschhorn Syndrome Candidate 1 (WHSC1, Accession NM\_007331), a gene which binds covalently to and repairs g/t mismatches. Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WHSC1. The function of WHSC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM200.Zinc Finger Protein 146 (ZNF146, Accession NM\_007145) is another VGAM567 host target gene. ZNF146 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ZNF146, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF146 BINDING SITE, designated SEQ ID:13996, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24577] Another function of VGAM567 is therefore inhibition of Zinc Finger Protein 146 (ZNF146, Accession NM\_007145), a gene which binds zinc ions, DNA, and heparin. Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF146. The function of ZNF146 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM192.ADP-ribosylation Factor Domain Protein 1, 64kDa (ARFD1, Accession NM\_001656) is another VGAM567 host target gene. ARFD1 BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by ARFD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARFD1 BINDING SITE, designated SEQ ID:7374, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24578] Another function of VGAM567 is therefore inhibition of ADP-ribosylation Factor Domain Protein 1, 64kDa (ARFD1, Accession NM\_001656). Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARFD1. BART1 (Accession NM\_012106) is another VGAM567 host target gene. BART1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BART1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BART1 BINDING SITE, designated SEQ ID:14426, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24579] Another function of VGAM567 is therefore inhibition of BART1 (Accession NM\_012106). Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BART1. FLJ20093 (Accession NM\_017664) is another VGAM567 host target gene. FLJ20093 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20093, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20093 BINDING SITE, designated SEQ ID:19206, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24580] Another function of VGAM567 is therefore inhibition of FLJ20093 (Accession NM\_017664). Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20093. KIAA0763 (Accession NM\_014869) is another VGAM567 host target gene. KIAA0763 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0763, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0763 BINDING SITE, designated SEQ ID:16966, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24581] Another function of VGAM567 is therefore inhibition of KIAA0763 (Accession NM\_014869). Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0763. Zinc Finger Protein 387 (ZNF387, Accession NM\_014682) is another VGAM567 host target gene. ZNF387 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF387, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF387 BINDING SITE, designated SEQ ID:16181, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24582] Another function of VGAM567 is therefore inhibition of Zinc Finger Protein 387 (ZNF387, Accession NM\_014682). Accordingly, utilities of VGAM567 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with ZNF387. LOC221830 (Accession XM\_166508) is another VGAM567 host target gene. LOC221830 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221830, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221830 BINDING SITE, designated SEQ ID:44437, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24583] Another function of VGAM567 is therefore inhibition of LOC221830 (Accession XM\_166508). Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221830. LOC222493 (Accession XM\_169446) is another VGAM567 host target gene. LOC222493 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC222493, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences



of LOC222493 BINDING SITE, designated SEQ ID:45302, to the nucleotide sequence of VGAM567 RNA, herein designated VGAM RNA, also designated SEQ ID:3278.

[24584] Another function of VGAM567 is therefore inhibition of LOC222493 (Accession XM\_169446). Accordingly, utilities of VGAM567 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222493. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 568 (VGAM568) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24585] VGAM568 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM568 was detected is described hereinabove with reference to Figs. 1–8.

[24586] VGAM568 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM568 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24587] VGAM568 gene encodes a VGAM568 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM568 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM568 precursor RNA is designated SEQ ID:554, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:554 is located at position 123346 relative to the genome of Fowlpox Virus.

[24588] VGAM568 precursor RNA folds onto itself, forming VGAM568 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24589] An enzyme complex designated DICER COMPLEX, `dices` the VGAM568 folded precursor RNA into VGAM568 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 49%) nucleotide sequence of VGAM568 RNA is designated SEQ ID:3279, and is provided hereinbelow with reference to the sequence listing part.

[24590] VGAM568 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM568 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM568 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24591] VGAM568 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM568 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM568 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM568 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM568 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24592] The complementary binding of VGAM568 RNA, herein designated VGAM RNA, to host target binding sites on VGAM568 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM568 host target RNA into VGAM568 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24593] It is appreciated that VGAM568 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM568 host target genes. The mRNA of each one of this plurality of VGAM568 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM568 RNA, herein designated VGAM RNA, and which when bound by VGAM568 RNA causes inhibition of translation of respective one or more VGAM568 host target proteins.

[24594] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM568 gene, herein designated VGAM GENE, on one or more VGAM568 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[24595] It is yet further appreciated that a function of VGAM568 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM568 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM568 correlate with, and may be deduced from, the identity of the host target genes which VGAM568 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24596] Nucleotide sequences of the VGAM568 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM568 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM568 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM568 are further described hereinbelow with reference to Table 1.

[24597] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM568 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM568 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24598] As mentioned hereinabove with reference to Fig. 1, a function of VGAM568 gene, herein designated VGAM is inhibition of expression of VGAM568 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM568 correlate with, and may be deduced from, the identity of the target genes which VGAM568 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24599] Fibroblast Growth Factor Receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome) (FGFR1, Accession NM\_000604) is a VGAM568 host target gene. FGFR1 BINDING SITE1 through FGFR1 BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGFR1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGFR1 BINDING SITE1 through FGFR1 BINDING SITE6, designated SEQ ID:6210, SEQ ID:17981, SEQ ID:23363, SEQ ID:23367, SEQ

ID:23378 and SEQ ID:23375 respectively, to the nucleotide sequence of VGAM568 RNA, herein designated VGAM RNA, also designated SEQ ID:3279.

[24600] A function of VGAM568 is therefore inhibition of Fibroblast Growth Factor Receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome) (FGFR1, Accession NM\_000604). Accordingly, utilities of VGAM568 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGFR1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 569 (VGAM569) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24601] VGAM569 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM569 was detected is described hereinabove with reference to Figs. 1–8.

[24602] VGAM569 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM569 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the



human genome.

[24603] VGAM569 gene encodes a VGAM569 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM569 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM569 precursor RNA is designated SEQ ID:555, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:555 is located at position 127302 relative to the genome of Fowlpox Virus.

[24604] VGAM569 precursor RNA folds onto itself, forming VGAM569 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24605] An enzyme complex designated DICER COMPLEX, `dices` the VGAM569 folded precursor RNA into VGAM569 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 56%) nucleotide sequence of VGAM569 RNA is designated SEQ ID:3280, and is provided hereinbelow with reference to the sequence listing part.

[24606] VGAM569 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM569 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM569 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24607] VGAM569 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM569 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM569 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM569 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM569 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24608] The complementary binding of VGAM569 RNA, herein designated VGAM RNA, to host target binding sites on VGAM569 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM569 host target RNA into VGAM569 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24609] It is appreciated that VGAM569 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM569 host target genes. The mRNA of each one of this plurality of VGAM569 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM569 RNA, herein designated VGAM RNA, and which when bound by VGAM569 RNA causes inhibition of translation of respective one or more VGAM569 host target proteins.

[24610] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM569 gene, herein designated VGAM GENE, on one or more VGAM569 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24611] It is yet further appreciated that a function of VGAM569 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM569 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM569 correlate with, and may be deduced from, the identity of the host target genes which VGAM569 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24612] Nucleotide sequences of the VGAM569 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM569 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM569 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM569 are further described hereinbelow with reference to Table 1.

[24613] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM569 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM569 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24614] As mentioned hereinabove with reference to Fig. 1, a function of VGAM569 gene, herein designated VGAM is inhibition of expression of VGAM569 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM569 correlate with, and may be deduced from, the identity of the target genes which VGAM569 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24615] UDP-  
N-  
acetyl-al-  
pha-  
D-galac-  
tosamine:(N-acetylneuraminy)-galactosylglucosylceramid  
e N-acetylgalactosaminyltransferase (GalNAc-T) (GALGT,  
Accession NM\_001478) is a VGAM569 host target gene.  
GALGT BINDING SITE is HOST TARGET binding site found  
in the 3' untranslated region of mRNA encoded by

GALGT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GALGT BINDING SITE, designated SEQ ID:7210, to the nucleotide sequence of VGAM569 RNA, herein designated VGAM RNA, also designated SEQ ID:3280.

[24616] A function of VGAM569 is therefore inhibition of UDP-N-acetyl-alpha-D-galactosamine:(N-acetylneuraminyl)-galactosylglucosylceramide N-acetylgalactosaminyltransferase (GalNAc-T) (GALGT, Accession NM\_001478), a gene which is involved in the biosynthesis of gangliosides gm2, gd2 and ga2. Accordingly, utilities of VGAM569 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GALGT. The function of GALGT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179.Homeo Box C10 (HOXC10, Accession XM\_028621) is another VGAM569

host target gene. HOXC10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HOXC10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HOXC10 BINDING SITE, designated SEQ ID:30720, to the nucleotide sequence of VGAM569 RNA, herein designated VGAM RNA, also designated SEQ ID:3280.

[24617] Another function of VGAM569 is therefore inhibition of Homeo Box C10 (HOXC10, Accession XM\_028621). Accordingly, utilities of VGAM569 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HOXC10. SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily D, Member 1 (SMARCD1, Accession NM\_003076) is another VGAM569 host target gene. SMARCD1 BINDING SITE1 and SMARCD1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SMARCD1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMARCD1 BINDING SITE1



and SMARCD1 BINDING SITE2, designated SEQ ID:9048 and SEQ ID:29146 respectively, to the nucleotide sequence of VGAM569 RNA, herein designated VGAM RNA, also designated SEQ ID:3280.

[24618] Another function of VGAM569 is therefore inhibition of SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily D, Member 1 (SMARCD1, Accession NM\_003076), a gene which is involved in chromatin assembly and remodeling. Accordingly, utilities of VGAM569 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMARCD1. The function of SMARCD1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152.LOC149628 (Accession XM\_086611) is another VGAM569 host target gene. LOC149628 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149628, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149628 BINDING SITE, designated SEQ ID:38791, to the nucleotide sequence of

VGAM569 RNA, herein designated VGAM RNA, also designated SEQ ID:3280.

[24619] Another function of VGAM569 is therefore inhibition of LOC149628 (Accession XM\_086611). Accordingly, utilities of VGAM569 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149628. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 570 (VGAM570) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24620] VGAM570 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM570 was detected is described hereinabove with reference to Figs. 1–8.

[24621] VGAM570 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM570 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24622] VGAM570 gene encodes a VGAM570 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM570 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM570 precursor RNA is designated SEQ ID:556, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:556 is located at position 124616 relative to the genome of Fowlpox Virus.

[24623] VGAM570 precursor RNA folds onto itself, forming VGAM570 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24624] An enzyme complex designated DICER COMPLEX, `dices` the VGAM570 folded precursor RNA into VGAM570 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM570 RNA is designated SEQ ID:3281, and is provided hereinbelow with reference to the sequence listing part.

[24625] VGAM570 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM570 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM570 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[24626] VGAM570 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM570 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM570 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM570 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM570 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24627] The complementary binding of VGAM570 RNA, herein designated VGAM RNA, to host target binding sites on VGAM570 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM570 host target RNA into VGAM570 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24628] It is appreciated that VGAM570 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM570 host target genes. The mRNA of each one of this plurality of VGAM570 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM570 RNA, herein designated VGAM RNA, and which when bound by VGAM570 RNA causes inhibition of translation of respective one or more VGAM570 host target proteins.

[24629] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM570 gene, herein designated VGAM GENE, on one or more VGAM570 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[24630] It is yet further appreciated that a function of VGAM570 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM570 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM570 correlate with, and may be deduced from, the identity of the host target genes which VGAM570 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[24631] Nucleotide sequences of the VGAM570 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM570 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM570 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM570 are further described hereinbelow with reference to Table 1.

[24632] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM570 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM570 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24633] As mentioned hereinabove with reference to Fig. 1, a function of VGAM570 gene, herein designated VGAM is inhibition of expression of VGAM570 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM570 correlate with, and may be deduced from, the identity of the target genes which VGAM570 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24634] UDP-Gal:betaGlcNAc Beta 1,3-galactosyltransferase, Polypeptide 2 (B3GALT2, Accession NM\_003783) is a VGAM570 host target gene. B3GALT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by B3GALT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B3GALT2 BINDING SITE, designated SEQ ID:9871, to the nucleotide sequence of VGAM570 RNA, herein designated VGAM RNA, also designated SEQ ID:3281.

[24635] A function of VGAM570 is therefore inhibition of UDP-



Gal:betaGlcNAc Beta 1,3-galactosyltransferase, Polypeptide 2 (B3GALT2, Accession NM\_003783). Accordingly, utilities of VGAM570 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B3GALT2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 571 (VGAM571) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24636] VGAM571 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM571 was detected is described hereinabove with reference to Figs. 1-8.

[24637] VGAM571 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM571 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24638] VGAM571 gene encodes a VGAM571 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM571

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM571 precursor RNA is designated SEQ ID:557, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:557 is located at position 152048 relative to the genome of Fowlpox Virus.

[24639] VGAM571 precursor RNA folds onto itself, forming VGAM571 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24640] An enzyme complex designated DICER COMPLEX, `dices` the VGAM571 folded precursor RNA into VGAM571 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 43%) nucleotide sequence of VGAM571 RNA is designated SEQ ID:3282, and is provided hereinbelow with reference to the sequence listing part.

[24641] VGAM571 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM571 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM571 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[24642] VGAM571 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM571 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM571 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM571 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM571 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24643] The complementary binding of VGAM571 RNA, herein designated VGAM RNA, to host target binding sites on VGAM571 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM571 host target RNA into VGAM571 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24644] It is appreciated that VGAM571 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM571 host target genes. The mRNA of each one of this plurality of VGAM571 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM571 RNA, herein designated VGAM RNA, and which when bound by VGAM571 RNA causes inhibition of translation of respective one or more VGAM571 host target proteins.

[24645] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM571 gene, herein designated VGAM GENE, on one or more VGAM571 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24646] It is yet further appreciated that a function of VGAM571 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM571 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM571 correlate with, and may be deduced from, the identity of the host target genes which VGAM571 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24647] Nucleotide sequences of the VGAM571 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM571 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM571 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM571 are further described hereinbelow with reference to Table 1.

[24648] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM571 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM571 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[24649] As mentioned hereinabove with reference to Fig. 1, a function of VGAM571 gene, herein designated VGAM is inhibition of expression of VGAM571 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM571 correlate with, and may be deduced from, the identity of the target genes which VGAM571 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24650] FLJ12448 (Accession NM\_022895) is a VGAM571 host target gene. FLJ12448 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12448, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12448 BINDING SITE, designated SEQ ID:23156, to the nucleotide sequence of VGAM571 RNA, herein designated VGAM RNA, also designated SEQ ID:3282.

[24651] A function of VGAM571 is therefore inhibition of FLJ12448 (Accession NM\_022895). Accordingly, utilities of VGAM571 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12448.

KIAA0293 (Accession XM\_027045) is another VGAM571 host target gene. KIAA0293 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0293, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0293 BINDING SITE, designated SEQ ID:30393, to the nucleotide sequence of VGAM571 RNA, herein designated VGAM RNA, also designated SEQ ID:3282.

[24652] Another function of VGAM571 is therefore inhibition of KIAA0293 (Accession XM\_027045). Accordingly, utilities of VGAM571 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0293. LOC152245 (Accession XM\_098182) is another VGAM571 host target gene. LOC152245 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152245, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152245 BINDING SITE, designated SEQ ID:41448, to the nucleotide sequence of VGAM571 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3282.

[24653] Another function of VGAM571 is therefore inhibition of LOC152245 (Accession XM\_098182). Accordingly, utilities of VGAM571 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152245. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 572 (VGAM572) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24654] VGAM572 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM572 was detected is described hereinabove with reference to Figs. 1–8.

[24655] VGAM572 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM572 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24656] VGAM572 gene encodes a VGAM572 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM572 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM572 precursor RNA is designated SEQ ID:558, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:558 is located at position 151611 relative to the genome of Fowlpox Virus.

[24657] VGAM572 precursor RNA folds onto itself, forming VGAM572 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24658] An enzyme complex designated DICER COMPLEX, `dices` the VGAM572 folded precursor RNA into VGAM572 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 63%) nucleotide sequence of VGAM572 RNA is designated SEQ ID:3283, and is provided hereinbelow with reference to the sequence listing part.

[24659] VGAM572 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM572 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM572 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24660] VGAM572 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM572 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM572 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM572 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM572 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24661] The complementary binding of VGAM572 RNA, herein designated VGAM RNA, to host target binding sites on VGAM572 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM572 host target RNA into VGAM572 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24662] It is appreciated that VGAM572 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM572 host target genes. The mRNA of

each one of this plurality of VGAM572 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM572 RNA, herein designated VGAM RNA, and which when bound by VGAM572 RNA causes inhibition of translation of respective one or more VGAM572 host target proteins.

[24663] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM572 gene, herein designated VGAM GENE, on one or more VGAM572 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[24664] It is yet further appreciated that a function of VGAM572 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM572 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM572 correlate with, and may be deduced from, the identity of the host target genes which VGAM572 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24665] Nucleotide sequences of the VGAM572 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM572 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM572 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM572 are further described hereinbelow with reference to Table 1.

[24666] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM572 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM572 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[24667] As mentioned hereinabove with reference to Fig. 1, a function of VGAM572 gene, herein designated VGAM is inhibition of expression of VGAM572 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM572 correlate with, and may be deduced from, the identity of the target genes which VGAM572 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24668] KIAA1948 (Accession XM\_091984) is a VGAM572 host target gene. KIAA1948 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1948, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1948 BINDING SITE, designated SEQ ID:40078, to the nucleotide sequence of VGAM572 RNA, herein designated VGAM RNA, also designated SEQ ID:3283.

[24669] A function of VGAM572 is therefore inhibition of KIAA1948 (Accession XM\_091984). Accordingly, utilities of VGAM572 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1948. RASD Family, Member 2 (RASD2, Accession NM\_014310) is another VGAM572 host target gene. RASD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RASD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASD2 BINDING SITE, designated SEQ ID:15599, to the nucleotide sequence of VGAM572 RNA, herein designated VGAM RNA, also designated SEQ ID:3283.

[24670] Another function of VGAM572 is therefore inhibition of RASD Family, Member 2 (RASD2, Accession NM\_014310). Accordingly, utilities of VGAM572 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASD2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 573 (VGAM573) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.



[24671] VGAM573 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM573 was detected is described hereinabove with reference to Figs. 1–8.

[24672] VGAM573 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM573 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24673] VGAM573 gene encodes a VGAM573 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM573 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM573 precursor RNA is designated SEQ ID:559, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:559 is located at position 150116 relative to the genome of Fowlpox Virus.

[24674] VGAM573 precursor RNA folds onto itself, forming VGAM573 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

‘hairpin structure’, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[24675] An enzyme complex designated DICER COMPLEX, ‘dices’ the VGAM573 folded precursor RNA into VGAM573 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, ‘dicing’ of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM573 RNA is designated SEQ ID:3284, and is provided hereinbelow with reference to the sequence listing part.

[24676] VGAM573 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM573 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM573 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5’ untranslated region, a protein coding region and a 3’ untranslated region, designated 5’UTR, PROTEIN

CODING and 3`UTR respectively.

[24677] VGAM573 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM573 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM573 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM573 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM573 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24678] The complementary binding of VGAM573 RNA, herein designated VGAM RNA, to host target binding sites on VGAM573 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM573 host target RNA into VGAM573 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24679] It is appreciated that VGAM573 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM573 host target genes. The mRNA of each one of this plurality of VGAM573 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM573 RNA, herein designated VGAM RNA, and which when bound by VGAM573 RNA causes inhibition of translation of respective one or more VGAM573 host target proteins.

[24680] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM573 gene, herein designated VGAM GENE, on one or more VGAM573 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24681] It is yet further appreciated that a function of VGAM573 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM573 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM573 correlate with, and may be deduced from, the identity of the host target genes which VGAM573 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24682] Nucleotide sequences of the VGAM573 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM573 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM573 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM573 are further  
described hereinbelow with reference to Table 1.

[24683] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM573 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM573 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[24684] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM573 gene, herein designated VGAM is  
inhibition of expression of VGAM573 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM573 correlate with, and may be deduced  
from, the identity of the target genes which VGAM573  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[24685] Zinc Finger Protein 268 (ZNF268, Accession XM\_031851)  
is a VGAM573 host target gene. ZNF268 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF268 BINDING SITE, designated SEQ ID:31498, to the nucleotide sequence of VGAM573 RNA, herein designated VGAM RNA, also designated SEQ ID:3284.

[24686] A function of VGAM573 is therefore inhibition of Zinc Finger Protein 268 (ZNF268, Accession XM\_031851). Accordingly, utilities of VGAM573 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF268. KIAA0970 (Accession NM\_014923) is another VGAM573 host target gene. KIAA0970 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0970, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0970 BINDING SITE, designated SEQ ID:17203, to the nucleotide sequence of VGAM573 RNA, herein designated VGAM RNA, also designated SEQ ID:3284.

[24687] Another function of VGAM573 is therefore inhibition of

KIAA0970 (Accession NM\_014923). Accordingly, utilities of VGAM573 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0970. TBC1 Domain Family, Member 2 (TBC1D2, Accession NM\_018421) is another VGAM573 host target gene. TBC1D2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TBC1D2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBC1D2 BINDING SITE, designated SEQ ID:20467, to the nucleotide sequence of VGAM573 RNA, herein designated VGAM RNA, also designated SEQ ID:3284.

[24688] Another function of VGAM573 is therefore inhibition of TBC1 Domain Family, Member 2 (TBC1D2, Accession NM\_018421). Accordingly, utilities of VGAM573 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TBC1D2. LOC92283 (Accession XM\_044049) is another VGAM573 host target gene. LOC92283 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92283, corresponding to a HOST TARGET binding



site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92283 BINDING SITE, designated SEQ ID:34092, to the nucleotide sequence of VGAM573 RNA, herein designated VGAM RNA, also designated SEQ ID:3284.

[24689] Another function of VGAM573 is therefore inhibition of LOC92283 (Accession XM\_044049). Accordingly, utilities of VGAM573 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92283. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 574 (VGAM574) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24690] VGAM574 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM574 was detected is described hereinabove with reference to Figs. 1–8.

[24691] VGAM574 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM574 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24692] VGAM574 gene encodes a VGAM574 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM574 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM574 precursor RNA is designated SEQ ID:560, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:560 is located at position 151276 relative to the genome of Fowlpox Virus.

[24693] VGAM574 precursor RNA folds onto itself, forming VGAM574 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24694] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM574 folded precursor RNA into VGAM574 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 77%) nucleotide sequence of VGAM574 RNA is designated SEQ ID:3285, and is provided hereinbelow with reference to the sequence listing part.

[24695] VGAM574 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM574 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM574 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24696] VGAM574 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM574 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM574 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM574 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM574 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24697] The complementary binding of VGAM574 RNA, herein designated VGAM RNA, to host target binding sites on VGAM574 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM574 host target RNA into VGAM574 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24698] It is appreciated that VGAM574 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM574 host target genes. The mRNA of each one of this plurality of VGAM574 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM574 RNA, herein designated VGAM RNA, and which when bound by VGAM574 RNA causes inhibition of translation of respective one or more VGAM574 host target proteins.

[24699] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM574 gene, herein designated VGAM GENE, on one or more VGAM574 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24700] It is yet further appreciated that a function of VGAM574 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM574 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM574 correlate with, and may be deduced from, the identity of the host target genes which VGAM574 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24701] Nucleotide sequences of the VGAM574 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM574 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM574 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM574 are further described hereinbelow with reference to Table 1.

[24702] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM574 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM574 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24703] As mentioned hereinabove with reference to Fig. 1, a function of VGAM574 gene, herein designated VGAM is inhibition of expression of VGAM574 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM574 correlate with, and may be deduced from, the identity of the target genes which VGAM574 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24704] Ceroid-lipofuscinosis, Neuronal 5 (CLN5, Accession NM\_006493) is a VGAM574 host target gene. CLN5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CLN5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLN5 BINDING SITE, designated SEQ ID:13225, to the nucleotide

sequence of VGAM574 RNA, herein designated VGAM RNA, also designated SEQ ID:3285.

[24705] A function of VGAM574 is therefore inhibition of Ceroid-lipofuscinosis, Neuronal 5 (CLN5, Accession NM\_006493). Accordingly, utilities of VGAM574 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLN5. FLJ13646 (Accession NM\_024584) is another VGAM574 host target gene. FLJ13646 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13646, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13646 BINDING SITE, designated SEQ ID:23810, to the nucleotide sequence of VGAM574 RNA, herein designated VGAM RNA, also designated SEQ ID:3285.

[24706] Another function of VGAM574 is therefore inhibition of FLJ13646 (Accession NM\_024584). Accordingly, utilities of VGAM574 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13646. KIAA1615 (Accession XM\_044021) is another VGAM574 host target gene. KIAA1615 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA



encoded by KIAA1615, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1615 BINDING SITE, designated SEQ ID:34081, to the nucleotide sequence of VGAM574 RNA, herein designated VGAM RNA, also designated SEQ ID:3285.

[24707] Another function of VGAM574 is therefore inhibition of KIAA1615 (Accession XM\_044021). Accordingly, utilities of VGAM574 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1615. Solute Carrier Family 21 (organic anion transporter), Member 14 (SLC21A14, Accession NM\_017435) is another VGAM574 host target gene. SLC21A14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC21A14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC21A14 BINDING SITE, designated SEQ ID:18891, to the nucleotide sequence of VGAM574 RNA, herein designated VGAM RNA, also designated SEQ ID:3285.

[24708] Another function of VGAM574 is therefore inhibition of

Solute Carrier Family 21 (organic anion transporter), Member 14 (SLC21A14, Accession NM\_017435). Accordingly, utilities of VGAM574 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC21A14. LOC146229 (Accession XM\_085387) is another VGAM574 host target gene. LOC146229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146229 BINDING SITE, designated SEQ ID:38115, to the nucleotide sequence of VGAM574 RNA, herein designated VGAM RNA, also designated SEQ ID:3285.

[24709] Another function of VGAM574 is therefore inhibition of LOC146229 (Accession XM\_085387). Accordingly, utilities of VGAM574 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146229. LOC92405 (Accession XM\_044914) is another VGAM574 host target gene. LOC92405 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92405, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92405 BINDING SITE, designated SEQ ID:34303, to the nucleotide sequence of VGAM574 RNA, herein designated VGAM RNA, also designated SEQ ID:3285.

[24710] Another function of VGAM574 is therefore inhibition of LOC92405 (Accession XM\_044914). Accordingly, utilities of VGAM574 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92405. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 575 (VGAM575) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24711] VGAM575 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM575 was detected is described hereinabove with reference to Figs. 1–8.

[24712] VGAM575 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM575 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[24713] VGAM575 gene encodes a VGAM575 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM575 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM575 precursor RNA is designated SEQ ID:561, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:561 is located at position 159770 relative to the genome of Fowlpox Virus.

[24714] VGAM575 precursor RNA folds onto itself, forming VGAM575 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24715] An enzyme complex designated DICER COMPLEX, `dices` the VGAM575 folded precursor RNA into VGAM575 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM575 RNA is designated SEQ ID:3286, and is provided hereinbelow with reference to the sequence listing part.

[24716] VGAM575 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM575 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM575 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24717] VGAM575 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM575 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM575 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM575 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM575 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24718] The complementary binding of VGAM575 RNA, herein designated VGAM RNA, to host target binding sites on VGAM575 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM575 host target RNA into VGAM575 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[24719] It is appreciated that VGAM575 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM575 host target genes. The mRNA of each one of this plurality of VGAM575 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM575 RNA, herein designated VGAM RNA, and which when bound by VGAM575 RNA causes inhibition of translation of respective one or more VGAM575 host target proteins.

[24720] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM575 gene, herein designated VGAM GENE, on one or more VGAM575 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24721] It is yet further appreciated that a function of VGAM575 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM575 correlate with, and may be deduced from, the identity of the host target genes which VGAM575 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24722] Nucleotide sequences of the VGAM575 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM575 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM575 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM575 are further described hereinbelow with reference to Table 1.

[24723] Nucleotide sequences of host target binding sites, such as



BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM575 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM575 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24724] As mentioned hereinabove with reference to Fig. 1, a function of VGAM575 gene, herein designated VGAM is inhibition of expression of VGAM575 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM575 correlate with, and may be deduced from, the identity of the target genes which VGAM575 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24725] Contactin Associated Protein-like 2 (CNTNAP2, Accession NM\_014141) is a VGAM575 host target gene. CNTNAP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNTNAP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNTNAP2 BINDING SITE, designated SEQ ID:15422, to the nucleotide sequence of VGAM575 RNA,

herein designated VGAM RNA, also designated SEQ ID:3286.

[24726] A function of VGAM575 is therefore inhibition of Contactin Associated Protein-like 2 (CNTNAP2, Accession NM\_014141). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNTNAP2. Eukaryotic Translation Initiation Factor 1A (EIF1A, Accession XM\_114147) is another VGAM575 host target gene. EIF1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF1A BINDING SITE, designated SEQ ID:42723, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24727] Another function of VGAM575 is therefore inhibition of Eukaryotic Translation Initiation Factor 1A (EIF1A, Accession XM\_114147), a gene which seems to be required for maximal rate of protein biosynthesis. Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF1A.

The function of EIF1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM120. Hematopoietically Expressed Homeobox (HHEX, Accession NM\_002729) is another VGAM575 host target gene. HHEX BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HHEX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HHEX BINDING SITE, designated SEQ ID:8595, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24728] Another function of VGAM575 is therefore inhibition of Hematopoietically Expressed Homeobox (HHEX, Accession NM\_002729), a gene which may play a role in hematopoietic differentiation. Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HHEX. The function of HHEX has been established by previous studies. Tanaka et al. (1999) found that rat HHEX functions as a transcriptional repressor in liver cells and may be involved in the

differentiation and/or maintenance of the differentiated state in hepatocytes. The divergent homeobox gene HEX is expressed in the anterior visceral endoderm during early mouse development and in some adult tissues of endodermal origin, including liver and thyroid. D'Elia et al. (2002) analyzed HEX expression and subcellular localization in a series of 55 human thyroid tumors and in several tumor cell lines. HEX mRNA was detected by RT-PCR either in normal tissues or in thyroid adenomas and differentiated (papillary and follicular) carcinomas. HEX mRNA was also expressed in most undifferentiated carcinomas. In normal tissues and adenomas, HEX protein was present both in nucleus and cytoplasm. In contrast, both differentiated and undifferentiated carcinomas, as well as the tumor cell lines investigated, showed HEX protein only in the cytoplasm. These findings suggested that regulation of HEX entry in the nucleus of thyrocytes may represent a critical step during human thyroid tumorigenesis.

[24729] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24730] Tanaka, T.; Inazu, T.; Yamada, K.; Myint, Z.; Keng, V. W; Inoue, Y.; Taniguchi, N.; Noguchi, T. : cDNA cloning and

expression of rat homeobox gene, Hex, and functional characterization of the protein. Biochem. J. 339: 111–117, 1999. ; and

[24731] D'Elia, A. V.; Tell, G.; Russo, D.; Arturi, F.; Puglisi, F.; Manfioletti, G.; Gattei, V.; Mack, D. L.; Cataldi, P.; Filetti, S.; Di Loreto, C.; Damante, G. : Expression and localization.

[24732] Further studies establishing the function and utilities of HHEX are found in John Hopkins OMIM database record ID 604420, and in cited publications numbered 7397–7402 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZp547H025 (Accession NM\_020161) is another VGAM575 host target gene. DKFZp547H025 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp547H025, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547H025 BINDING SITE, designated SEQ ID:21372, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24733] Another function of VGAM575 is therefore inhibition of DKFZp547H025 (Accession NM\_020161). Accordingly,

utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547H025. DKFZp761B0514 (Accession NM\_032289) is another VGAM575 host target gene. DKFZp761B0514 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp761B0514, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761B0514 BINDING SITE, designated SEQ ID:26050, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24734] Another function of VGAM575 is therefore inhibition of DKFZp761B0514 (Accession NM\_032289). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761B0514. Eukaryotic Translation Initiation Factor 2, Subunit 1 Alpha, 35kDa (EIF2S1, Accession NM\_004094) is another VGAM575 host target gene. EIF2S1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF2S1, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF2S1 BINDING SITE, designated SEQ ID:10299, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24735] Another function of VGAM575 is therefore inhibition of Eukaryotic Translation Initiation Factor 2, Subunit 1 Alpha, 35kDa (EIF2S1, Accession NM\_004094). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF2S1. KIAA0008 (Accession NM\_014750) is another VGAM575 host target gene. KIAA0008 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0008, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0008 BINDING SITE, designated SEQ ID:16461, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24736] Another function of VGAM575 is therefore inhibition of KIAA0008 (Accession NM\_014750). Accordingly, utilities

of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0008. KIAA1673 (Accession XM\_047672) is another VGAM575 host target gene. KIAA1673 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1673, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1673 BINDING SITE, designated SEQ ID:35026, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24737] Another function of VGAM575 is therefore inhibition of KIAA1673 (Accession XM\_047672). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1673. KIAA1911 (Accession XM\_056302) is another VGAM575 host target gene. KIAA1911 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1911, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of



KIAA1911 BINDING SITE, designated SEQ ID:36392, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24738] Another function of VGAM575 is therefore inhibition of KIAA1911 (Accession XM\_056302). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1911. Signal Sequence Receptor, Gamma (translocon-associated protein gamma) (SSR3, Accession NM\_007107) is another VGAM575 host target gene. SSR3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSR3 BINDING SITE, designated SEQ ID:13974, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24739] Another function of VGAM575 is therefore inhibition of Signal Sequence Receptor, Gamma (translocon-associated protein gamma) (SSR3, Accession NM\_007107). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with SSR3. LOC147341 (Accession XM\_097223) is another VGAM575 host target gene. LOC147341 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147341, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147341 BINDING SITE, designated SEQ ID:40829, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24740] Another function of VGAM575 is therefore inhibition of LOC147341 (Accession XM\_097223). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147341. LOC148195 (Accession XM\_097419) is another VGAM575 host target gene. LOC148195 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148195, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148195 BINDING SITE, designated SEQ ID:40875, to the nucleotide sequence of VGAM575 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3286.

[24741] Another function of VGAM575 is therefore inhibition of LOC148195 (Accession XM\_097419). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148195. LOC158819 (Accession XM\_098995) is another VGAM575 host target gene. LOC158819 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158819, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158819 BINDING SITE, designated SEQ ID:42028, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24742] Another function of VGAM575 is therefore inhibition of LOC158819 (Accession XM\_098995). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158819. LOC51026 (Accession NM\_016072) is another VGAM575 host target gene. LOC51026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51026, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51026 BINDING SITE, designated SEQ ID:18141, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24743] Another function of VGAM575 is therefore inhibition of LOC51026 (Accession NM\_016072). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51026. LOC91035 (Accession XM\_035622) is another VGAM575 host target gene. LOC91035 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91035, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91035 BINDING SITE, designated SEQ ID:32291, to the nucleotide sequence of VGAM575 RNA, herein designated VGAM RNA, also designated SEQ ID:3286.

[24744] Another function of VGAM575 is therefore inhibition of LOC91035 (Accession XM\_035622). Accordingly, utilities of VGAM575 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC91035. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 576 (VGAM576) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24745] VGAM576 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM576 was detected is described hereinabove with reference to Figs. 1–8.

[24746] VGAM576 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM576 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24747] VGAM576 gene encodes a VGAM576 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM576 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM576 precursor RNA is designated SEQ

ID:562, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:562 is located at position 160178 relative to the genome of Fowlpox Virus.

[24748] VGAM576 precursor RNA folds onto itself, forming VGAM576 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24749] An enzyme complex designated DICER COMPLEX, `dices` the VGAM576 folded precursor RNA into VGAM576 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM576 RNA is designated SEQ ID:3287, and is provided hereinbelow with reference to the sequence

listing part.

[24750] VGAM576 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM576 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM576 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24751] VGAM576 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM576 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM576 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM576 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM576 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24752] The complementary binding of VGAM576 RNA, herein designated VGAM RNA, to host target binding sites on VGAM576 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM576 host target RNA into VGAM576 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24753] It is appreciated that VGAM576 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM576 host target genes. The mRNA of each one of this plurality of VGAM576 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM576 RNA, herein designated VGAM



RNA, and which when bound by VGAM576 RNA causes inhibition of translation of respective one or more VGAM576 host target proteins.

[24754] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM576 gene, herein designated VGAM GENE, on one or more VGAM576 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24755] It is yet further appreciated that a function of VGAM576 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM576 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM576 correlate with, and may be deduced from, the identity of the host target genes which VGAM576 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24756] Nucleotide sequences of the VGAM576 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM576 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM576 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM576 are further described hereinbelow with reference to Table 1.

[24757] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM576 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM576 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24758] As mentioned hereinabove with reference to Fig. 1, a function of VGAM576 gene, herein designated VGAM is

inhibition of expression of VGAM576 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM576 correlate with, and may be deduced from, the identity of the target genes which VGAM576 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24759] Sorbitol Dehydrogenase (SORD, Accession NM\_003104) is a VGAM576 host target gene. SORD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SORD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SORD BINDING SITE, designated SEQ ID:9069, to the nucleotide sequence of VGAM576 RNA, herein designated VGAM RNA, also designated SEQ ID:3287.

[24760] A function of VGAM576 is therefore inhibition of Sorbitol Dehydrogenase (SORD, Accession NM\_003104). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORD. Wilms Tumor 1 (WT1, Accession NM\_024424) is another VGAM576 host target gene. WT1 BINDING SITE1 through WT1 BINDING SITE4 are HOST

TARGET binding sites found in untranslated regions of mRNA encoded by WT1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WT1 BINDING SITE1 through WT1 BINDING SITE4, designated SEQ ID:23666, SEQ ID:5950, SEQ ID:23670 and SEQ ID:23674 respectively, to the nucleotide sequence of VGAM576 RNA, herein designated VGAM RNA, also designated SEQ ID:3287.

[24761] Another function of VGAM576 is therefore inhibition of Wilms Tumor 1 (WT1, Accession NM\_024424). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WT1. FLJ11011 (Accession NM\_018299) is another VGAM576 host target gene. FLJ11011 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11011, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11011 BINDING SITE, designated SEQ ID:20290, to the nucleotide sequence of VGAM576 RNA, herein designated VGAM

RNA, also designated SEQ ID:3287.

[24762] Another function of VGAM576 is therefore inhibition of FLJ11011 (Accession NM\_018299). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11011. FLJ20802 (Accession NM\_017959) is another VGAM576 host target gene. FLJ20802 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20802, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20802 BINDING SITE, designated SEQ ID:19673, to the nucleotide sequence of VGAM576 RNA, herein designated VGAM RNA, also designated SEQ ID:3287.

[24763] Another function of VGAM576 is therefore inhibition of FLJ20802 (Accession NM\_017959). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20802. KIAA1396 (Accession XM\_032054) is another VGAM576 host target gene. KIAA1396 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1396, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1396 BINDING SITE, designated SEQ ID:31547, to the nucleotide sequence of VGAM576 RNA, herein designated VGAM RNA, also designated SEQ ID:3287.

[24764] Another function of VGAM576 is therefore inhibition of KIAA1396 (Accession XM\_032054). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1396. LOC116166 (Accession XM\_007651) is another VGAM576 host target gene. LOC116166 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC116166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC116166 BINDING SITE, designated SEQ ID:30059, to the nucleotide sequence of VGAM576 RNA, herein designated VGAM RNA, also designated SEQ ID:3287.

[24765] Another function of VGAM576 is therefore inhibition of LOC116166 (Accession XM\_007651). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC116166. LOC201696 (Accession XM\_032269) is another VGAM576 host target gene. LOC201696 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201696 BINDING SITE, designated SEQ ID:31624, to the nucleotide sequence of VGAM576 RNA, herein designated VGAM RNA, also designated SEQ ID:3287.

[24766] Another function of VGAM576 is therefore inhibition of LOC201696 (Accession XM\_032269). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201696. LOC254266 (Accession XM\_173221) is another VGAM576 host target gene. LOC254266 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254266, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254266 BINDING SITE, designated SEQ ID:46479, to

the nucleotide sequence of VGAM576 RNA, herein designated VGAM RNA, also designated SEQ ID:3287.

[24767] Another function of VGAM576 is therefore inhibition of LOC254266 (Accession XM\_173221). Accordingly, utilities of VGAM576 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254266. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 577 (VGAM577) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24768] VGAM577 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM577 was detected is described hereinabove with reference to Figs. 1–8.

[24769] VGAM577 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM577 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24770] VGAM577 gene encodes a VGAM577 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM577 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM577 precursor RNA is designated SEQ ID:563, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:563 is located at position 170504 relative to the genome of Fowlpox Virus.

[24771] VGAM577 precursor RNA folds onto itself, forming VGAM577 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24772] An enzyme complex designated DICER COMPLEX, `dices` the VGAM577 folded precursor RNA into VGAM577 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM577 RNA is designated SEQ ID:3288, and is provided hereinbelow with reference to the sequence listing part.

[24773] VGAM577 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM577 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM577 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[24774] VGAM577 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM577 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM577 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM577 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM577 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24775] The complementary binding of VGAM577 RNA, herein designated VGAM RNA, to host target binding sites on VGAM577 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM577 host target RNA into VGAM577 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24776] It is appreciated that VGAM577 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM577 host target genes. The mRNA of each one of this plurality of VGAM577 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM577 RNA, herein designated VGAM RNA, and which when bound by VGAM577 RNA causes inhibition of translation of respective one or more VGAM577 host target proteins.

[24777] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM577 gene, herein designated VGAM GENE, on one or more VGAM577 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[24778] It is yet further appreciated that a function of VGAM577 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM577 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM577 correlate with, and may be deduced from, the identity of the host target genes which VGAM577 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[24779] Nucleotide sequences of the VGAM577 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM577 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM577 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM577 are further described hereinbelow with reference to Table 1.

[24780] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM577 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM577 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24781] As mentioned hereinabove with reference to Fig. 1, a function of VGAM577 gene, herein designated VGAM is inhibition of expression of VGAM577 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM577 correlate with, and may be deduced from, the identity of the target genes which VGAM577 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24782] TOX (Accession NM\_014729) is a VGAM577 host target gene. TOX BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TOX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOX BINDING SITE, designated SEQ ID:16325, to the nucleotide sequence of VGAM577 RNA, herein designated VGAM RNA, also designated SEQ ID:3288.

[24783] A function of VGAM577 is therefore inhibition of TOX (Accession NM\_014729). Accordingly, utilities of VGAM577 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with TOX.

Ubiquitin-like 3 (UBL3, Accession NM\_007106) is another VGAM577 host target gene. UBL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBL3 BINDING SITE, designated SEQ ID:13965, to the nucleotide sequence of VGAM577 RNA, herein designated VGAM RNA, also designated SEQ ID:3288.

[24784] Another function of VGAM577 is therefore inhibition of Ubiquitin-like 3 (UBL3, Accession NM\_007106), a gene which appears to have a diverse range of cellular functions. Accordingly, utilities of VGAM577 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBL3. The function of UBL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM459.DKFZP547E2110 (Accession XM\_165676) is another VGAM577 host target gene. DKFZP547E2110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by DKFZP547E2110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP547E2110 BINDING SITE, designated SEQ ID:43731, to the nucleotide sequence of VGAM577 RNA, herein designated VGAM RNA, also designated SEQ ID:3288.

[24785] Another function of VGAM577 is therefore inhibition of DKFZP547E2110 (Accession XM\_165676). Accordingly, utilities of VGAM577 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP547E2110. FLJ10352 (Accession NM\_032142) is another VGAM577 host target gene. FLJ10352 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10352, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10352 BINDING SITE, designated SEQ ID:25828, to the nucleotide sequence of VGAM577 RNA, herein designated VGAM RNA, also designated SEQ ID:3288.

[24786] Another function of VGAM577 is therefore inhibition of FLJ10352 (Accession NM\_032142). Accordingly, utilities of



VGAM577 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10352. KIAA1028 (Accession XM\_166324) is another VGAM577 host target gene. KIAA1028 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1028 BINDING SITE, designated SEQ ID:44166, to the nucleotide sequence of VGAM577 RNA, herein designated VGAM RNA, also designated SEQ ID:3288.

[24787] Another function of VGAM577 is therefore inhibition of KIAA1028 (Accession XM\_166324). Accordingly, utilities of VGAM577 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1028. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 578 (VGAM578) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24788] VGAM578 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM578 was detected is described hereinabove with reference to Figs. 1–8.

[24789] VGAM578 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM578 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24790] VGAM578 gene encodes a VGAM578 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM578 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM578 precursor RNA is designated SEQ ID:564, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:564 is located at position 168962 relative to the genome of Fowlpox Virus.

[24791] VGAM578 precursor RNA folds onto itself, forming VGAM578 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24792] An enzyme complex designated DICER COMPLEX, `dices` the VGAM578 folded precursor RNA into VGAM578 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM578 RNA is designated SEQ ID:3289, and is provided hereinbelow with reference to the sequence listing part.

[24793] VGAM578 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM578 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM578 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[24794] VGAM578 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM578 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM578 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM578 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM578 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24795] The complementary binding of VGAM578 RNA, herein designated VGAM RNA, to host target binding sites on VGAM578 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM578 host target RNA into VGAM578 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24796] It is appreciated that VGAM578 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM578 host target genes. The mRNA of each one of this plurality of VGAM578 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM578 RNA, herein designated VGAM RNA, and which when bound by VGAM578 RNA causes inhibition of translation of respective one or more VGAM578 host target proteins.

[24797] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM578 gene, herein designated VGAM GENE, on one or more VGAM578 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24798] It is yet further appreciated that a function of VGAM578 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM578 correlate with, and may be deduced from, the identity of the host target genes which VGAM578 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24799] Nucleotide sequences of the VGAM578 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM578 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM578 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM578 are further  
described hereinbelow with reference to Table 1.

[24800] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM578 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM578 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[24801] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM578 gene, herein designated VGAM is  
inhibition of expression of VGAM578 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM578 correlate with, and may be deduced  
from, the identity of the target genes which VGAM578  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[24802] Calcium/calmodulin-dependent Protein Kinase IV (CAMK4,  
Accession NM\_001744) is a VGAM578 host target gene.

CAMK4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAMK4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAMK4 BINDING SITE, designated SEQ ID:7482, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24803] A function of VGAM578 is therefore inhibition of Calcium/calmodulin-dependent Protein Kinase IV (CAMK4, Accession NM\_001744), a gene which is a heat-stable, acidic, calmodulin-binding protein. Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAMK4. The function of CAMK4 has been established by previous studies. Protein phosphorylation, a prominent activity in the brain, apparently plays an important role in several neural functions such as neural transmitter release, ion channel modulation, and axoplasmic transport. Sikela et al. (1989) identified cDNA clones corresponding to a brain Ca(2+)/calmodulin-dependent protein kinase, which they referred to as brain CaM kinase IV (CAMK4). On the basis



of Western blot analysis, this kinase appeared to be restricted to brain in the rat; interestingly, it was not detected in the brain of the newborn, but became detectable within a few days after birth. Animal model experiments lend further support to the function of CAMK4. Camk4 is a multifunctional serine/threonine protein kinase with limited tissue distribution that has been implicated in transcriptional regulation in lymphocytes, neurons, and male germ cells. In the mouse testis, however, Camk4 is expressed in spermatids and associated with chromatin and nuclear matrix. Elongating spermatids are not transcriptionally active, raising the possibility that Camk4 has a novel function in male germ cells. To investigate the role of Camk4 in spermatogenesis, Wu et al. (2000) generated mice with a targeted deletion of the Camk4 gene. Male Camk4  $-/-$  mice were infertile with impairment of spermiogenesis in late elongating spermatids. The sequential deposition of sperm basic nuclear proteins on chromatin was disrupted, with a specific loss of protamine-2 (OMIM Ref. No. 182890) and prolonged retention of transition protein-2 (OMIM Ref. No. 190232) in step-15 spermatids. Protamine-2 is phosphorylated by Camk4 in vitro, implicating a connection between Camk4

signaling and the exchange of basic nuclear proteins in mammalian male germ cells. Defects in protamine-2 have been identified in sperm of infertile men, suggesting that the results of Wu et al. (2000) may have clinical implications for the understanding of human male infertility.

[24804] It is appreciated that the abovementioned animal model for CAMK4 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[24805] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24806] Sikela, J. M.; Law, M. L.; Kao, F.-T.; Hartz, J. A.; Wei, Q.; Hahn, W. E. : Chromosomal localization of the human gene for brain Ca(2+)/calmodulin-dependent protein kinase type IV. *Genomics* 4: 21-27, 1989. ; and

[24807] Wu, J. Y.; Ribar, T. J.; Cummings, D. E.; Burton, K. A.; McKnight, G. S.; Means, A. R. : Spermiogenesis and exchange of basic nuclear proteins are impaired in male germ cells lacking Cam.

[24808] Further studies establishing the function and utilities of CAMK4 are found in John Hopkins OMIM database record ID 114080, and in cited publications numbered

12075–12081 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Down Syndrome Critical Region Gene 1–like 1 (DSCR1L1, Accession NM\_005822) is another VGAM578 host target gene. DSCR1L1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DSCR1L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DSCR1L1 BINDING SITE, designated SEQ ID:12431, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24809] Another function of VGAM578 is therefore inhibition of Down Syndrome Critical Region Gene 1–like 1 (DSCR1L1, Accession NM\_005822). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSCR1L1.

FLJ13646 (Accession NM\_024584) is another VGAM578 host target gene. FLJ13646 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13646, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13646 BINDING SITE, designated SEQ ID:23814, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24810] Another function of VGAM578 is therefore inhibition of FLJ13646 (Accession NM\_024584). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13646. FLJ14106 (Accession NM\_025067) is another VGAM578 host target gene. FLJ14106 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14106 BINDING SITE, designated SEQ ID:24663, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24811] Another function of VGAM578 is therefore inhibition of FLJ14106 (Accession NM\_025067). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14106.

KIAA0515 (Accession XM\_033380) is another VGAM578 host target gene. KIAA0515 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0515, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0515 BINDING SITE, designated SEQ ID:31928, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24812] Another function of VGAM578 is therefore inhibition of KIAA0515 (Accession XM\_033380). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0515. KIAA1554 (Accession XM\_170834) is another VGAM578 host target gene. KIAA1554 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1554, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1554 BINDING SITE, designated SEQ ID:45612, to the nucleotide sequence of VGAM578 RNA, herein designated

VGAM RNA, also designated SEQ ID:3289.

[24813] Another function of VGAM578 is therefore inhibition of KIAA1554 (Accession XM\_170834). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1554. Suppression of Tumorigenicity 13 (colon carcinoma) (Hsp70 interacting protein) (ST13, Accession NM\_003932) is another VGAM578 host target gene. ST13 BINDING SITE1 and ST13 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ST13, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ST13 BINDING SITE1 and ST13 BINDING SITE2, designated SEQ ID:10032 and SEQ ID:10033 respectively, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24814] Another function of VGAM578 is therefore inhibition of Suppression of Tumorigenicity 13 (colon carcinoma) (Hsp70 interacting protein) (ST13, Accession NM\_003932). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with ST13. LOC157798 (Accession XM\_098827) is another VGAM578 host target gene. LOC157798 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157798, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157798 BINDING SITE, designated SEQ ID:41851, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24815] Another function of VGAM578 is therefore inhibition of LOC157798 (Accession XM\_098827). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157798. LOC163590 (Accession NM\_145034) is another VGAM578 host target gene. LOC163590 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC163590, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163590 BINDING SITE, designated SEQ ID:29652, to the nucleotide sequence of VGAM578 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3289.

[24816] Another function of VGAM578 is therefore inhibition of LOC163590 (Accession NM\_145034). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163590. LOC255045 (Accession XM\_171243) is another VGAM578 host target gene. LOC255045 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255045, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255045 BINDING SITE, designated SEQ ID:46034, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24817] Another function of VGAM578 is therefore inhibition of LOC255045 (Accession XM\_171243). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255045. LOC51134 (Accession NM\_016122) is another VGAM578 host target gene. LOC51134 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51134, corre-



sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51134 BINDING SITE, designated SEQ ID:18207, to the nucleotide sequence of VGAM578 RNA, herein designated VGAM RNA, also designated SEQ ID:3289.

[24818] Another function of VGAM578 is therefore inhibition of LOC51134 (Accession NM\_016122). Accordingly, utilities of VGAM578 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51134. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 579 (VGAM579) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24819] VGAM579 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM579 was detected is described hereinabove with reference to Figs. 1–8.

[24820] VGAM579 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM579 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24821] VGAM579 gene encodes a VGAM579 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM579 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM579 precursor RNA is designated SEQ ID:565, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:565 is located at position 219679 relative to the genome of Fowlpox Virus.

[24822] VGAM579 precursor RNA folds onto itself, forming VGAM579 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24823] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM579 folded precursor RNA into VGAM579 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 89%) nucleotide sequence of VGAM579 RNA is designated SEQ ID:3290, and is provided hereinbelow with reference to the sequence listing part.

[24824] VGAM579 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM579 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM579 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24825] VGAM579 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM579 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM579 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM579 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM579 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24826] The complementary binding of VGAM579 RNA, herein designated VGAM RNA, to host target binding sites on VGAM579 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM579 host target RNA into VGAM579 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24827] It is appreciated that VGAM579 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM579 host target genes. The mRNA of each one of this plurality of VGAM579 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM579 RNA, herein designated VGAM RNA, and which when bound by VGAM579 RNA causes inhibition of translation of respective one or more VGAM579 host target proteins.

[24828] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM579 gene, herein designated VGAM GENE, on one or more VGAM579 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24829] It is yet further appreciated that a function of VGAM579 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM579 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM579 correlate with, and may be deduced from, the identity of the host target genes which VGAM579 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24830] Nucleotide sequences of the VGAM579 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM579 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM579 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM579 are further described hereinbelow with reference to Table 1.

[24831] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM579 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM579 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24832] As mentioned hereinabove with reference to Fig. 1, a function of VGAM579 gene, herein designated VGAM is inhibition of expression of VGAM579 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM579 correlate with, and may be deduced from, the identity of the target genes which VGAM579 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24833] Adducin 3 (gamma) (ADD3, Accession NM\_016824) is a VGAM579 host target gene. ADD3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADD3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADD3 BINDING SITE, designated SEQ ID:18818, to the nucleotide sequence of

VGAM579 RNA, herein designated VGAM RNA, also designated SEQ ID:3290.

[24834] A function of VGAM579 is therefore inhibition of Adducin 3 (gamma) (ADD3, Accession NM\_016824), a gene which membrane-cytoskeleton-associated protein that promotes the assembly of the spectrin-actin network. Accordingly, utilities of VGAM579 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADD3. The function of ADD3 has been established by previous studies. From a human fetal-brain cDNA library, Katagiri et al. (1996) isolated a novel human cDNA which they termed adducin-like 70. The predicted amino acid sequence shows a high degree of homology to adducins (alpha- 102680; beta- 102681). In human erythrocytes, adducin is a 200-kD heterodimeric skeletal component of the cell membrane, where it promotes the binding of spectrin to actin. This binding is regulated by calcium/calmodulin (OMIM Ref. No. 114180). Adducin also is phosphorylated by protein kinase-C. Adducin and its multiple isoforms represent a family of proteins present in a variety of tissues and cultured cell lines, including those from brain, kidney, and liver. The gene, symbolized here ADDL, contains an open reading frame of 2,022 nu-



cleotides encoding 674 amino acids. It shows 54%, 53%, and 59% identity in predicted amino acid sequence with alpha and beta components of human adducin and rat adducin 63, respectively. Katagiri et al. (1996) stated that human adducin-like 70 is likely to play an important role in the skeletal organization of the cell membrane. Northern blot analysis indicated ubiquitous expression of this gene in adult human tissues. In a comprehensive assay of gene expression, Gilligan et al. (1999) showed the ubiquitous expression of alpha- and gamma-adducin, in contrast to the restricted expression of beta-adducin. Beta-adducin was expressed at high levels in brain and hematopoietic tissues (bone marrow in humans, spleen in mice).

[24835] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24836] Gilligan, D. M.; Lozovatsky, L.; Gwynn, B.; Brugnara, C.; Mohandas, N.; Peters, L. L. : Targeted disruption of the beta adducin gene (Add2) causes red blood cell spherocytosis in mice. Proc. Nat. Acad. Sci. 96: 10717-10722, 1999. ; and

[24837] Katagiri, T.; Ozaki, K.; Fujiwara, T.; Shimizu, F.; Kawai, A.;

Okuno, S.; Suzuki, M.; Nakamura, Y.; Takahashi, E.; Hirai, Y. : Cloning, expression and chromosome mapping of ad-  
ducin-lik.

[24838] Further studies establishing the function and utilities of  
ADD3 are found in John Hopkins OMIM database record ID  
601568, and in cited publications numbered 2791–2792  
listed in the bibliography section hereinbelow, which are  
also hereby incorporated by reference. Activator of Basal  
Transcription 1 (ABT1, Accession NM\_013375) is another  
VGAM579 host target gene. ABT1 BINDING SITE is HOST  
TARGET binding site found in the 3` untranslated region  
of mRNA encoded by ABT1, corresponding to a HOST  
TARGET binding site such as BINDING SITE I, BINDING SITE  
II or BINDING SITE III. Table 2 illustrates the complemen-  
tarity of the nucleotide sequences of ABT1 BINDING SITE,  
designated SEQ ID:15028, to the nucleotide sequence of  
VGAM579 RNA, herein designated VGAM RNA, also desig-  
nated SEQ ID:3290.

[24839] Another function of VGAM579 is therefore inhibition of  
Activator of Basal Transcription 1 (ABT1, Accession  
NM\_013375). Accordingly, utilities of VGAM579 include  
diagnosis, prevention and treatment of diseases and clini-  
cal conditions associated with ABT1. FLJ21144 (Accession

NM\_022774) is another VGAM579 host target gene. FLJ21144 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21144, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21144 BINDING SITE, designated SEQ ID:23039, to the nucleotide sequence of VGAM579 RNA, herein designated VGAM RNA, also designated SEQ ID:3290.

[24840] Another function of VGAM579 is therefore inhibition of FLJ21144 (Accession NM\_022774). Accordingly, utilities of VGAM579 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21144. FLJ22551 (Accession NM\_024708) is another VGAM579 host target gene. FLJ22551 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ22551, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22551 BINDING SITE, designated SEQ ID:24026, to the nucleotide sequence of VGAM579 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3290.

[24841] Another function of VGAM579 is therefore inhibition of FLJ22551 (Accession NM\_024708). Accordingly, utilities of VGAM579 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22551. KIAA0594 (Accession XM\_036117) is another VGAM579 host target gene. KIAA0594 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0594, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0594 BINDING SITE, designated SEQ ID:32384, to the nucleotide sequence of VGAM579 RNA, herein designated VGAM RNA, also designated SEQ ID:3290.

[24842] Another function of VGAM579 is therefore inhibition of KIAA0594 (Accession XM\_036117). Accordingly, utilities of VGAM579 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0594. KIAA1877 (Accession XM\_038616) is another VGAM579 host target gene. KIAA1877 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1877, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1877 BINDING SITE, designated SEQ ID:32883, to the nucleotide sequence of VGAM579 RNA, herein designated VGAM RNA, also designated SEQ ID:3290.

[24843] Another function of VGAM579 is therefore inhibition of KIAA1877 (Accession XM\_038616). Accordingly, utilities of VGAM579 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1877. TNF Receptor-associated Factor 3 (TRAF3, Accession XM\_007256) is another VGAM579 host target gene. TRAF3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRAF3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRAF3 BINDING SITE, designated SEQ ID:30045, to the nucleotide sequence of VGAM579 RNA, herein designated VGAM RNA, also designated SEQ ID:3290.

[24844] Another function of VGAM579 is therefore inhibition of TNF Receptor-associated Factor 3 (TRAF3, Accession

XM\_007256). Accordingly, utilities of VGAM579 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRAF3. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 580 (VGAM580) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24845] VGAM580 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM580 was detected is described hereinabove with reference to Figs. 1–8.

[24846] VGAM580 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM580 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24847] VGAM580 gene encodes a VGAM580 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM580 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM580 precursor RNA is designated SEQ ID:566, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:566 is located at position 244009 relative to the genome of Fowlpox Virus.

[24848] VGAM580 precursor RNA folds onto itself, forming VGAM580 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24849] An enzyme complex designated DICER COMPLEX, `dices` the VGAM580 folded precursor RNA into VGAM580 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 77%) nucleotide sequence of VGAM580 RNA is designated SEQ ID:3291, and

is provided hereinbelow with reference to the sequence listing part.

[24850] VGAM580 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM580 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM580 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[24851] VGAM580 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM580 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM580 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-



ing – VGAM580 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM580 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24852] The complementary binding of VGAM580 RNA, herein designated VGAM RNA, to host target binding sites on VGAM580 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM580 host target RNA into VGAM580 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24853] It is appreciated that VGAM580 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM580 host target genes. The mRNA of each one of this plurality of VGAM580 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM580 RNA, herein designated VGAM RNA, and which when bound by VGAM580 RNA causes inhibition of translation of respective one or more VGAM580 host target proteins.

[24854] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM580 gene, herein designated VGAM GENE, on one or more VGAM580 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24855] It is yet further appreciated that a function of VGAM580 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM580 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM580 correlate with, and may be deduced from, the identity of the host target genes which VGAM580 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24856] Nucleotide sequences of the VGAM580 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM580 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM580 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM580 are further described hereinbelow with reference to Table 1.

[24857] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM580 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM580 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24858] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM580 gene, herein designated VGAM is inhibition of expression of VGAM580 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM580 correlate with, and may be deduced from, the identity of the target genes which VGAM580 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24859] Solute Carrier Family 15 (oligopeptide transporter), Member 1 (SLC15A1, Accession NM\_005073) is a VGAM580 host target gene. SLC15A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC15A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC15A1 BINDING SITE, designated SEQ ID:11520, to the nucleotide sequence of VGAM580 RNA, herein designated VGAM RNA, also designated SEQ ID:3291.

[24860] A function of VGAM580 is therefore inhibition of Solute Carrier Family 15 (oligopeptide transporter), Member 1 (SLC15A1, Accession NM\_005073), a gene which is a H(+)-coupled peptide transporter. Accordingly, utilities of VGAM580 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with SLC15A1. The function of SLC15A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74.FLJ10846 (Accession NM\_018241) is another VGAM580 host target gene. FLJ10846 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10846, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10846 BINDING SITE, designated SEQ ID:20201, to the nucleotide sequence of VGAM580 RNA, herein designated VGAM RNA, also designated SEQ ID:3291.

[24861] Another function of VGAM580 is therefore inhibition of FLJ10846 (Accession NM\_018241). Accordingly, utilities of VGAM580 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10846. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 581 (VGAM581) viral gene, which modulates expression of respective host target genes thereof, the function and

utility of which host target genes is known in the art.

[24862] VGAM581 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM581 was detected is described hereinabove with reference to Figs. 1–8.

[24863] VGAM581 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM581 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24864] VGAM581 gene encodes a VGAM581 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM581 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM581 precursor RNA is designated SEQ ID:567, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:567 is located at position 244236 relative to the genome of Fowlpox Virus.

[24865] VGAM581 precursor RNA folds onto itself, forming VGAM581 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[24866] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM581 folded precursor RNA into VGAM581 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 91%) nucleotide se-  
quence of VGAM581 RNA is designated SEQ ID:3292, and  
is provided hereinbelow with reference to the sequence  
listing part.

[24867] VGAM581 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM581 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM581 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[24868] VGAM581 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM581 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM581 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM581 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM581 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR



and 5`UTR regions.

[24869] The complementary binding of VGAM581 RNA, herein designated VGAM RNA, to host target binding sites on VGAM581 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM581 host target RNA into VGAM581 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24870] It is appreciated that VGAM581 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM581 host target genes. The mRNA of each one of this plurality of VGAM581 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM581 RNA, herein designated VGAM RNA, and which when bound by VGAM581 RNA causes inhibition of translation of respective one or more VGAM581 host target proteins.

[24871] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM581 gene, herein designated VGAM GENE, on one or

more VGAM581 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24872] It is yet further appreciated that a function of VGAM581 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM581 correlate with, and may be deduced from, the identity of the host target genes which VGAM581 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [24873] Nucleotide sequences of the VGAM581 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM581 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM581 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM581 are further described hereinbelow with reference to Table 1.
- [24874] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM581 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM581 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [24875] As mentioned hereinabove with reference to Fig. 1, a function of VGAM581 gene, herein designated VGAM is inhibition of expression of VGAM581 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM581 correlate with, and may be deduced from, the identity of the target genes which VGAM581 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [24876] CASP8 Associated Protein 2 (CASP8AP2, Accession

NM\_012115) is a VGAM581 host target gene. CASP8AP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CASP8AP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CASP8AP2 BINDING SITE, designated SEQ ID:14429, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24877] A function of VGAM581 is therefore inhibition of CASP8 Associated Protein 2 (CASP8AP2, Accession NM\_012115), a gene which interacts with and activates caspase-8 in Fas-mediated apoptosis. Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CASP8AP2. The function of CASP8AP2 has been established by previous studies. Through coimmunoprecipitation and transfection experiments, Imai et al. (1999) determined that Flash binds caspase-8 (OMIM Ref. No. 601763) and Fadd (OMIM Ref. No. 602457). It also specifically coimmunoprecipitated with activated Fas (OMIM Ref. No. 134637), suggesting that Casp8ap2 is part of the

death-inducing signaling complex (DISC). Using luciferase reporter analysis, Choi et al. (2001) showed that inhibition of FLASH expression abolishes TNF (OMIM Ref. No. 191160)-induced NF $\kappa$ B (OMIM Ref. No. 164011) activation in embryonic kidney cells. Expression or overexpression of FLASH activates NF $\kappa$ B through a central oligomerization domain, called the NF $\kappa$ B activation domain (NAD), in a TRAF2 (OMIM Ref. No. 601895)-NIK (OMIM Ref. No. 604655)-IKKA (OMIM Ref. No. 600664)-dependent pathway. Immunoprecipitation analysis indicated that the FLASH NAD interacts with TRAF2. Choi et al. (2001) concluded that FLASH coordinates downstream NF $\kappa$ B activity via a TRAF2-dependent pathway in TNF signaling.

[24878] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24879] Choi, Y.-H.; Kim, K.-B.; Kim, H.-H.; Hong, G.-S.; Kwon, Y.-K.; Chung, C.-W.; Park, Y.-M.; Shen, Z.-J.; Kim, B. J.; Lee, S.-Y.; Jung, Y.-K. : FLASH coordinates NF- $\kappa$ B activity via TRAF2. J. Biol. Chem. 276: 25073-25077, 2001. ; and

[24880] Imai, Y.; Kimura, T.; Murakami, A.; Yajima, N.; Sakamaki, K.; Yonehara, S. : The CED-4-homologous protein FLASH

is involved in Fas-mediated activation of caspase-8 during apoptosis. Na.

[24881] Further studies establishing the function and utilities of CASP8AP2 are found in John Hopkins OMIM database record ID 606880, and in cited publications numbered 6083-6084 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Dual Adaptor of Phosphotyrosine and 3-phosphoinositides (DAPP1, Accession NM\_014395) is another VGAM581 host target gene. DAPP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DAPP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAPP1 BINDING SITE, designated SEQ ID:15732, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24882] Another function of VGAM581 is therefore inhibition of Dual Adaptor of Phosphotyrosine and 3-phosphoinositides (DAPP1, Accession NM\_014395), a gene which regulates the ras-cyclic amp pathway. Accordingly, utilities of VGAM581 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with DAPP1. The function of DAPP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM283.FLJ10483 (Accession NM\_018108) is another VGAM581 host target gene. FLJ10483 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10483, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10483 BINDING SITE, designated SEQ ID:19878, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24883] Another function of VGAM581 is therefore inhibition of FLJ10483 (Accession NM\_018108). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10483. FLJ10936 (Accession NM\_018279) is another VGAM581 host target gene. FLJ10936 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10936, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10936 BINDING SITE, designated SEQ ID:20272, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24884] Another function of VGAM581 is therefore inhibition of FLJ10936 (Accession NM\_018279). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10936. KIAA0798 (Accession NM\_014650) is another VGAM581 host target gene. KIAA0798 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0798, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0798 BINDING SITE, designated SEQ ID:16070, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24885] Another function of VGAM581 is therefore inhibition of KIAA0798 (Accession NM\_014650). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with KIAA0798. TERA (Accession NM\_021238) is another VGAM581 host target gene. TERA BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TERA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TERA BINDING SITE, designated SEQ ID:22207, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24886] Another function of VGAM581 is therefore inhibition of TERA (Accession NM\_021238). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TERA. Zinc Finger Protein 84 (HPF2) (ZNF84, Accession NM\_003428) is another VGAM581 host target gene. ZNF84 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZNF84, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF84 BINDING SITE, designated SEQ ID:9478,

to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24887] Another function of VGAM581 is therefore inhibition of Zinc Finger Protein 84 (HPF2) (ZNF84, Accession NM\_003428). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF84. LOC127255 (Accession NM\_145258) is another VGAM581 host target gene. LOC127255 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC127255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127255 BINDING SITE, designated SEQ ID:29774, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24888] Another function of VGAM581 is therefore inhibition of LOC127255 (Accession NM\_145258). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127255. LOC90317 (Accession XM\_030892) is another VGAM581 host target gene. LOC90317 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC90317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90317 BINDING SITE, designated SEQ ID:31208, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24889] Another function of VGAM581 is therefore inhibition of LOC90317 (Accession XM\_030892). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90317. LOC93070 (Accession XM\_049046) is another VGAM581 host target gene. LOC93070 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC93070, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93070 BINDING SITE, designated SEQ ID:35327, to the nucleotide sequence of VGAM581 RNA, herein designated VGAM RNA, also designated SEQ ID:3292.

[24890] Another function of VGAM581 is therefore inhibition of

LOC93070 (Accession XM\_049046). Accordingly, utilities of VGAM581 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93070. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 582 (VGAM582) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24891] VGAM582 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM582 was detected is described hereinabove with reference to Figs. 1–8.

[24892] VGAM582 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM582 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24893] VGAM582 gene encodes a VGAM582 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM582 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM582 precursor RNA is designated SEQ ID:568, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:568 is located at position 251054 relative to the genome of Fowlpox Virus.

[24894] VGAM582 precursor RNA folds onto itself, forming VGAM582 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24895] An enzyme complex designated DICER COMPLEX, `dices` the VGAM582 folded precursor RNA into VGAM582 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide se-

quence of VGAM582 RNA is designated SEQ ID:3293, and is provided hereinbelow with reference to the sequence listing part.

[24896] VGAM582 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM582 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM582 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[24897] VGAM582 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM582 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM582 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM582 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM582 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24898] The complementary binding of VGAM582 RNA, herein designated VGAM RNA, to host target binding sites on VGAM582 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM582 host target RNA into VGAM582 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24899] It is appreciated that VGAM582 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM582 host target genes. The mRNA of each one of this plurality of VGAM582 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM582 RNA, herein designated VGAM RNA, and which when bound by VGAM582 RNA causes inhibition of translation of respective one or more VGAM582 host target proteins.

[24900] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM582 gene, herein designated VGAM GENE, on one or more VGAM582 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24901] It is yet further appreciated that a function of VGAM582 is



inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM582 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM582 correlate with, and may be deduced from, the identity of the host target genes which VGAM582 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24902] Nucleotide sequences of the VGAM582 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM582 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM582 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM582 are further described hereinbelow with reference to Table 1.

[24903] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM582 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM582 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24904] As mentioned hereinabove with reference to Fig. 1, a function of VGAM582 gene, herein designated VGAM is inhibition of expression of VGAM582 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM582 correlate with, and may be deduced from, the identity of the target genes which VGAM582 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24905] Mitochondrial Translational Initiation Factor 2 (MTIF2, Accession NM\_002453) is a VGAM582 host target gene. MTIF2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MTIF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTIF2 BINDING SITE, designated SEQ ID:8289, to the nucleotide sequence of VGAM582 RNA, herein designated VGAM RNA, also designated SEQ ID:3293.

[24906] A function of VGAM582 is therefore inhibition of Mitochondrial Translational Initiation Factor 2 (MTIF2, Accession NM\_002453). Accordingly, utilities of VGAM582 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTIF2. Zinc Finger Pro-

tein 202 (ZNF202, Accession NM\_003455) is another VGAM582 host target gene. ZNF202 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF202, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF202 BINDING SITE, designated SEQ ID:9507, to the nucleotide sequence of VGAM582 RNA, herein designated VGAM RNA, also designated SEQ ID:3293.

[24907] Another function of VGAM582 is therefore inhibition of Zinc Finger Protein 202 (ZNF202, Accession NM\_003455). Accordingly, utilities of VGAM582 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF202. CG012 (Accession XM\_096710) is another VGAM582 host target gene. CG012 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CG012, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CG012 BINDING SITE, designated SEQ ID:40484, to the nucleotide sequence of VGAM582 RNA, herein designated VGAM RNA,

also designated SEQ ID:3293.

[24908] Another function of VGAM582 is therefore inhibition of CG012 (Accession XM\_096710). Accordingly, utilities of VGAM582 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CG012. DKFZP564C196 (Accession XM\_046405) is another VGAM582 host target gene. DKFZP564C196 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP564C196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564C196 BINDING SITE, designated SEQ ID:34710, to the nucleotide sequence of VGAM582 RNA, herein designated VGAM RNA, also designated SEQ ID:3293.

[24909] Another function of VGAM582 is therefore inhibition of DKFZP564C196 (Accession XM\_046405). Accordingly, utilities of VGAM582 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564C196. Polymerase (RNA) II (DNA directed) Polypeptide D (POLR2D, Accession NM\_004805) is another VGAM582 host target gene. POLR2D BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by POLR2D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POLR2D BINDING SITE, designated SEQ ID:11228, to the nucleotide sequence of VGAM582 RNA, herein designated VGAM RNA, also designated SEQ ID:3293.

[24910] Another function of VGAM582 is therefore inhibition of Polymerase (RNA) II (DNA directed) Polypeptide D (POLR2D, Accession NM\_004805). Accordingly, utilities of VGAM582 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POLR2D. TPARG (Accession NM\_018475) is another VGAM582 host target gene. TPARG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TPARG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TPARG BINDING SITE, designated SEQ ID:20542, to the nucleotide sequence of VGAM582 RNA, herein designated VGAM RNA, also designated SEQ ID:3293.

[24911] Another function of VGAM582 is therefore inhibition of

TPARL (Accession NM\_018475). Accordingly, utilities of VGAM582 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TPARL.

Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 583 (VGAM583) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24912] VGAM583 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM583 was detected is described hereinabove with reference to Figs. 1–8.

[24913] VGAM583 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM583 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24914] VGAM583 gene encodes a VGAM583 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM583 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM583 precursor RNA is designated SEQ ID:569, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:569 is located at position 274080 relative to the genome of Fowlpox Virus.

[24915] VGAM583 precursor RNA folds onto itself, forming VGAM583 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24916] An enzyme complex designated DICER COMPLEX, `dices` the VGAM583 folded precursor RNA into VGAM583 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM583 RNA is designated SEQ ID:3294, and

is provided hereinbelow with reference to the sequence listing part.

[24917] VGAM583 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM583 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM583 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24918] VGAM583 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM583 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM583 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-



ing – VGAM583 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM583 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24919] The complementary binding of VGAM583 RNA, herein designated VGAM RNA, to host target binding sites on VGAM583 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM583 host target RNA into VGAM583 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24920] It is appreciated that VGAM583 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM583 host target genes. The mRNA of each one of this plurality of VGAM583 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM583 RNA, herein designated VGAM RNA, and which when bound by VGAM583 RNA causes inhibition of translation of respective one or more VGAM583 host target proteins.

[24921] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM583 gene, herein designated VGAM GENE, on one or more VGAM583 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24922] It is yet further appreciated that a function of VGAM583 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM583 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM583 correlate with, and may be deduced from, the identity of the host target genes which VGAM583 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24923] Nucleotide sequences of the VGAM583 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM583 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM583 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM583 are further described hereinbelow with reference to Table 1.

[24924] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM583 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM583 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24925] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM583 gene, herein designated VGAM is inhibition of expression of VGAM583 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM583 correlate with, and may be deduced from, the identity of the target genes which VGAM583 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24926] Interleukin 12 Receptor, Beta 2 (IL12RB2, Accession NM\_001559) is a VGAM583 host target gene. IL12RB2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by IL12RB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL12RB2 BINDING SITE, designated SEQ ID:7281, to the nucleotide sequence of VGAM583 RNA, herein designated VGAM RNA, also designated SEQ ID:3294.

[24927] A function of VGAM583 is therefore inhibition of Interleukin 12 Receptor, Beta 2 (IL12RB2, Accession NM\_001559), a gene which is involved in il-12 transduction. binds to il-12 with a low affinity. Accordingly, utilities of VGAM583 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with IL12RB2. The function of IL12RB2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM326.FLJ00024 (Accession XM\_033361) is another VGAM583 host target gene. FLJ00024 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ00024, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ00024 BINDING SITE, designated SEQ ID:31887, to the nucleotide sequence of VGAM583 RNA, herein designated VGAM RNA, also designated SEQ ID:3294.

[24928] Another function of VGAM583 is therefore inhibition of FLJ00024 (Accession XM\_033361). Accordingly, utilities of VGAM583 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00024. LOC121536 (Accession XM\_058567) is another VGAM583 host target gene. LOC121536 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC121536, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC121536 BINDING SITE, designated SEQ ID:36663, to the nucleotide sequence of VGAM583 RNA, herein designated VGAM RNA, also designated SEQ ID:3294.

[24929] Another function of VGAM583 is therefore inhibition of LOC121536 (Accession XM\_058567). Accordingly, utilities of VGAM583 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC121536. LOC221322 (Accession XM\_166323) is another VGAM583 host target gene. LOC221322 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221322 BINDING SITE, designated SEQ ID:44152, to the nucleotide sequence of VGAM583 RNA, herein designated VGAM RNA, also designated SEQ ID:3294.

[24930] Another function of VGAM583 is therefore inhibition of LOC221322 (Accession XM\_166323). Accordingly, utilities of VGAM583 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC221322. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 584 (VGAM584) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24931] VGAM584 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM584 was detected is described hereinabove with reference to Figs. 1–8.

[24932] VGAM584 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM584 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24933] VGAM584 gene encodes a VGAM584 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM584 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM584 precursor RNA is designated SEQ ID:570, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:570 is located at position 54006 relative to the genome of Fowlpox Virus.

[24934] VGAM584 precursor RNA folds onto itself, forming VGAM584 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24935] An enzyme complex designated DICER COMPLEX, `dices` the VGAM584 folded precursor RNA into VGAM584 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM584 RNA is designated SEQ ID:3295, and is provided hereinbelow with reference to the sequence listing part.



[24936] VGAM584 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM584 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM584 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24937] VGAM584 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM584 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM584 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM584 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM584 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24938] The complementary binding of VGAM584 RNA, herein designated VGAM RNA, to host target binding sites on VGAM584 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM584 host target RNA into VGAM584 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24939] It is appreciated that VGAM584 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM584 host target genes. The mRNA of each one of this plurality of VGAM584 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM584 RNA, herein designated VGAM RNA, and which when bound by VGAM584 RNA causes in-

hibition of translation of respective one or more VGAM584 host target proteins.

[24940] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM584 gene, herein designated VGAM GENE, on one or more VGAM584 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24941] It is yet further appreciated that a function of VGAM584 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM584 include diagnosis, prevention and

treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM584 correlate with, and may be deduced from, the identity of the host target genes which VGAM584 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [24942] Nucleotide sequences of the VGAM584 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM584 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM584 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM584 are further described hereinbelow with reference to Table 1.
- [24943] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM584 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM584 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [24944] As mentioned hereinabove with reference to Fig. 1, a function of VGAM584 gene, herein designated VGAM is inhibition of expression of VGAM584 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM584 correlate with, and may be deduced from, the identity of the target genes which VGAM584 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24945] Desmoplakin (DPI, DPII) (DSP, Accession NM\_004415) is a VGAM584 host target gene. DSP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DSP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DSP BINDING SITE, designated SEQ ID:10678, to the nucleotide sequence of VGAM584 RNA, herein designated VGAM RNA, also designated SEQ ID:3295.

[24946] A function of VGAM584 is therefore inhibition of Desmoplakin (DPI, DPII) (DSP, Accession NM\_004415). Accordingly, utilities of VGAM584 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSP. Retinoic Acid Induced 2 (RAI2, Accession NM\_021785) is another VGAM584 host target gene. RAI2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RAI2, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAI2 BINDING SITE, designated SEQ ID:22350, to the nucleotide sequence of VGAM584 RNA, herein designated VGAM RNA, also designated SEQ ID:3295.

[24947] Another function of VGAM584 is therefore inhibition of Retinoic Acid Induced 2 (RAI2, Accession NM\_021785). Accordingly, utilities of VGAM584 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAI2. Dual-specificity tyrosine-(Y)-phosphorylation Regulated Kinase 4 (DYRK4, Accession XM\_034551) is another VGAM584 host target gene. DYRK4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DYRK4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DYRK4 BINDING SITE, designated SEQ ID:32123, to the nucleotide sequence of VGAM584 RNA, herein designated VGAM RNA, also designated SEQ ID:3295.

[24948] Another function of VGAM584 is therefore inhibition of

Dual-specificity tyrosine-(Y)-phosphorylation Regulated Kinase 4 (DYRK4, Accession XM\_034551). Accordingly, utilities of VGAM584 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DYRK4. FLJ21032 (Accession NM\_024906) is another VGAM584 host target gene. FLJ21032 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21032 BINDING SITE, designated SEQ ID:24401, to the nucleotide sequence of VGAM584 RNA, herein designated VGAM RNA, also designated SEQ ID:3295.

[24949] Another function of VGAM584 is therefore inhibition of FLJ21032 (Accession NM\_024906). Accordingly, utilities of VGAM584 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21032. LOC219942 (Accession XM\_167790) is another VGAM584 host target gene. LOC219942 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219942, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219942 BINDING SITE, designated SEQ ID:44826, to the nucleotide sequence of VGAM584 RNA, herein designated VGAM RNA, also designated SEQ ID:3295.

[24950] Another function of VGAM584 is therefore inhibition of LOC219942 (Accession XM\_167790). Accordingly, utilities of VGAM584 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219942. LOC221288 (Accession XM\_168058) is another VGAM584 host target gene. LOC221288 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221288, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221288 BINDING SITE, designated SEQ ID:44973, to the nucleotide sequence of VGAM584 RNA, herein designated VGAM RNA, also designated SEQ ID:3295.

[24951] Another function of VGAM584 is therefore inhibition of LOC221288 (Accession XM\_168058). Accordingly, utilities of VGAM584 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC221288. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 585 (VGAM585) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24952] VGAM585 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM585 was detected is described hereinabove with reference to Figs. 1–8.

[24953] VGAM585 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM585 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24954] VGAM585 gene encodes a VGAM585 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM585 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM585 precursor RNA is designated SEQ ID:571, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:571 is located at position 24033 relative to the genome of Gallid Herpesvirus 2.

[24955] VGAM585 precursor RNA folds onto itself, forming VGAM585 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24956] An enzyme complex designated DICER COMPLEX, `dices` the VGAM585 folded precursor RNA into VGAM585 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 62%) nucleotide sequence of VGAM585 RNA is designated SEQ ID:3296, and is provided hereinbelow with reference to the sequence listing part.

[24957] VGAM585 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM585 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM585 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[24958] VGAM585 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM585 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM585 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM585 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM585 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[24959] The complementary binding of VGAM585 RNA, herein designated VGAM RNA, to host target binding sites on VGAM585 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM585 host target RNA into VGAM585 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24960] It is appreciated that VGAM585 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM585 host target genes. The mRNA of each one of this plurality of VGAM585 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM585 RNA, herein designated VGAM RNA, and which when bound by VGAM585 RNA causes in-

hibition of translation of respective one or more VGAM585 host target proteins.

[24961] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM585 gene, herein designated VGAM GENE, on one or more VGAM585 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24962] It is yet further appreciated that a function of VGAM585 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM585 include diagnosis, prevention and

treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM585 correlate with, and may be deduced from, the identity of the host target genes which VGAM585 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24963] Nucleotide sequences of the VGAM585 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM585 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM585 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM585 are further described hereinbelow with reference to Table 1.

[24964] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM585 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM585 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[24965] As mentioned hereinabove with reference to Fig. 1, a function of VGAM585 gene, herein designated VGAM is inhibition of expression of VGAM585 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM585 correlate with, and may be deduced from, the identity of the target genes which VGAM585 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[24966] EGF-like-domain, Multiple 5 (EGFL5, Accession XM\_098838) is a VGAM585 host target gene. EGFL5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EGFL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGFL5 BINDING SITE, designated SEQ ID:41875, to the nucleotide sequence of VGAM585 RNA, herein designated VGAM RNA, also designated SEQ ID:3296.

[24967] A function of VGAM585 is therefore inhibition of EGF-like-domain, Multiple 5 (EGFL5, Accession XM\_098838). Accordingly, utilities of VGAM585 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGFL5. LOC165552 (Accession XM\_092666) is another VGAM585 host target gene. LOC165552 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

LOC165552, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC165552 BINDING SITE, designated SEQ ID:40131, to the nucleotide sequence of VGAM585 RNA, herein designated VGAM RNA, also designated SEQ ID:3296.

[24968] Another function of VGAM585 is therefore inhibition of LOC165552 (Accession XM\_092666). Accordingly, utilities of VGAM585 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC165552. LOC200132 (Accession XM\_114126) is another VGAM585 host target gene. LOC200132 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200132, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200132 BINDING SITE, designated SEQ ID:42710, to the nucleotide sequence of VGAM585 RNA, herein designated VGAM RNA, also designated SEQ ID:3296.

[24969] Another function of VGAM585 is therefore inhibition of LOC200132 (Accession XM\_114126). Accordingly, utilities



of VGAM585 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200132. LOC93380 (Accession XM\_051020) is another VGAM585 host target gene. LOC93380 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93380, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93380 BINDING SITE, designated SEQ ID:35724, to the nucleotide sequence of VGAM585 RNA, herein designated VGAM RNA, also designated SEQ ID:3296.

[24970] Another function of VGAM585 is therefore inhibition of LOC93380 (Accession XM\_051020). Accordingly, utilities of VGAM585 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93380. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 586 (VGAM586) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24971] VGAM586 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM586 was detected is described hereinabove with reference to Figs. 1–8.

[24972] VGAM586 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM586 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[24973] VGAM586 gene encodes a VGAM586 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM586 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM586 precursor RNA is designated SEQ ID:572, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:572 is located at position 25576 relative to the genome of Gallid Herpesvirus 2.

[24974] VGAM586 precursor RNA folds onto itself, forming VGAM586 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[24975] An enzyme complex designated DICER COMPLEX, `dices` the VGAM586 folded precursor RNA into VGAM586 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 62%) nucleotide sequence of VGAM586 RNA is designated SEQ ID:3297, and is provided hereinbelow with reference to the sequence listing part.

[24976] VGAM586 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM586 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM586 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[24977] VGAM586 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM586 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM586 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM586 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM586 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[24978] The complementary binding of VGAM586 RNA, herein designated VGAM RNA, to host target binding sites on VGAM586 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM586 host target RNA into VGAM586 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[24979] It is appreciated that VGAM586 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM586 host target genes. The mRNA of each one of this plurality of VGAM586 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM586 RNA, herein designated VGAM RNA, and which when bound by VGAM586 RNA causes inhibition of translation of respective one or more VGAM586 host target proteins.

[24980] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM586 gene, herein designated VGAM GENE, on one or more VGAM586 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[24981] It is yet further appreciated that a function of VGAM586 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM586 correlate with, and may be deduced from, the identity of the host target genes which VGAM586 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[24982] Nucleotide sequences of the VGAM586 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM586 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM586 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM586 are further  
described hereinbelow with reference to Table 1.

[24983] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM586 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM586 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[24984] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM586 gene, herein designated VGAM is  
inhibition of expression of VGAM586 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM586 correlate with, and may be deduced  
from, the identity of the target genes which VGAM586  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[24985] Amiloride-sensitive Cation Channel 2, Neuronal (ACCN2,  
Accession NM\_020039) is a VGAM586 host target gene.

ACCN2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ACCN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACCN2 BINDING SITE, designated SEQ ID:21297, to the nucleotide sequence of VGAM586 RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24986] A function of VGAM586 is therefore inhibition of Amiloride-sensitive Cation Channel 2, Neuronal (ACCN2, Accession NM\_020039). Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACCN2. COX11 Homolog, Cytochrome C Oxidase Assembly Protein (yeast) (COX11, Accession NM\_004375) is another VGAM586 host target gene. COX11 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by COX11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COX11 BINDING SITE, designated SEQ ID:10592, to the nucleotide sequence of VGAM586



RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24987] Another function of VGAM586 is therefore inhibition of COX11 Homolog, Cytochrome C Oxidase Assembly Protein (yeast) (COX11, Accession NM\_004375). Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COX11. NORE1 (Accession NM\_031437) is another VGAM586 host target gene. NORE1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NORE1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NORE1 BINDING SITE, designated SEQ ID:25443, to the nucleotide sequence of VGAM586 RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24988] Another function of VGAM586 is therefore inhibition of NORE1 (Accession NM\_031437), a gene which may modulate intracellular signal transduction pathways. Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NORE1. The function of NORE1 and its associa-

tion with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM276. Solute Carrier Family 14 (urea transporter), Member 1 (Kidd blood group) (SLC14A1, Accession NM\_015865) is another VGAM586 host target gene. SLC14A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC14A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC14A1 BINDING SITE, designated SEQ ID:17996, to the nucleotide sequence of VGAM586 RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24989] Another function of VGAM586 is therefore inhibition of Solute Carrier Family 14 (urea transporter), Member 1 (Kidd blood group) (SLC14A1, Accession NM\_015865), a gene which is a urea transporters in spermatogenesis. Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC14A1. The function of SLC14A1 has been established by previous studies. Tsukaguchi et al. (1997) undertook a characterization of the tissue distribution and

physiologic role of the erythrocyte urea transporter, UT11, by studying its rat homolog and testing whether there are additional urea transporter isoforms expressed in rat kidney. Using a PCR-based homology cloning approach with degenerate primers corresponding to conserved regions of the UT family of genes, they isolated a kidney urea transporter that appeared to be the rat homolog of human UT11. The rat gene, symbolized UT3 by them, was strongly expressed in the kidney. Furthermore, UT3 was expressed in testis, brain, bone marrow, and spleen. Its expression in the rat testis suggested a potential role for urea transporters in spermatogenesis. On in situ hybridization of testis, UT3 was detected in Sertoli cells associated with the early stages of spermatocyte development. The distribution in the kidneys suggested that UT3 is involved in counter-current exchange between ascending and descending vasa recta, to enhance the corticopapillary osmolality gradient. Although Jk-null red blood cells have reduced urea permeability, the Jk deficiency is not associated with any obvious clinical syndrome except for a urine concentration defect (Sands et al., 1992) that probably results from the absence of the Jk protein expressed on endothelial cells of the vasa recta of kidney

(Xu et al., 1997; Promeneur et al., 1996). Persons with the Jk-null phenotype are detected because antibody against Jk3 can develop after immunization by transfusion or pregnancy, and this antibody may cause immediate and delayed hemolytic transfusion reactions (Lucien et al. (2002)).

[24990] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[24991] Tsukaguchi, H.; Shayakul, C.; Berger, U. V.; Tokui, T.; Brown, D.; Hediger, M. A. : Cloning and characterization of the urea transportation UT3: localization in rat kidney and testis. J. Clin. Invest. 99: 1506–1515, 1997. ; and

[24992] Sands, J. M.; Gargus, J. J.; Frohlich, O.; Gunn, R. B.; Kokko, J. P. : Urinary concentrating ability in patients with Jk(a/b) blood type who lack carrier-mediated urea transport. J. Am. Soc.

[24993] Further studies establishing the function and utilities of SLC14A1 are found in John Hopkins OMIM database record ID 111000, and in cited publications numbered 12376–12090, 9433, 12091, 12092–12094, 11251, 12095–22 and 3780–234 listed in the bibliography section hereinbelow, which are also hereby incorporated by

reference. Chromosome 6 Open Reading Frame 26 (C6orf26, Accession NM\_025259) is another VGAM586 host target gene. C6orf26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C6orf26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C6orf26 BINDING SITE, designated SEQ ID:24929, to the nucleotide sequence of VGAM586 RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24994] Another function of VGAM586 is therefore inhibition of Chromosome 6 Open Reading Frame 26 (C6orf26, Accession NM\_025259). Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C6orf26. FLJ20188 (Accession NM\_017703) is another VGAM586 host target gene. FLJ20188 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20188, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20188 BINDING SITE, designated

SEQ ID:19275, to the nucleotide sequence of VGAM586 RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24995] Another function of VGAM586 is therefore inhibition of FLJ20188 (Accession NM\_017703). Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20188. LOC221143 (Accession XM\_167986) is another VGAM586 host target gene. LOC221143 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221143, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221143 BINDING SITE, designated SEQ ID:44945, to the nucleotide sequence of VGAM586 RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24996] Another function of VGAM586 is therefore inhibition of LOC221143 (Accession XM\_167986). Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221143. LOC253918 (Accession XM\_171345) is another VGAM586 host target gene. LOC253918 BINDING

SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253918, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253918 BINDING SITE, designated SEQ ID:46042, to the nucleotide sequence of VGAM586 RNA, herein designated VGAM RNA, also designated SEQ ID:3297.

[24997] Another function of VGAM586 is therefore inhibition of LOC253918 (Accession XM\_171345). Accordingly, utilities of VGAM586 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253918. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 587 (VGAM587) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[24998] VGAM587 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM587 was detected is described hereinabove with reference to Figs. 1-8.

[24999] VGAM587 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM587 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25000] VGAM587 gene encodes a VGAM587 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM587 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM587 precursor RNA is designated SEQ ID:573, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:573 is located at position 24271 relative to the genome of Gallid Herpesvirus 2.

[25001] VGAM587 precursor RNA folds onto itself, forming VGAM587 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-



cleotide sequence of the second half thereof.

[25002] An enzyme complex designated DICER COMPLEX, `dices` the VGAM587 folded precursor RNA into VGAM587 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM587 RNA is designated SEQ ID:3298, and is provided hereinbelow with reference to the sequence listing part.

[25003] VGAM587 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM587 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM587 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25004] VGAM587 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM587 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM587 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM587 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM587 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[25005] The complementary binding of VGAM587 RNA, herein designated VGAM RNA, to host target binding sites on VGAM587 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM587 host target RNA into VGAM587 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25006] It is appreciated that VGAM587 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM587 host target genes. The mRNA of each one of this plurality of VGAM587 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM587 RNA, herein designated VGAM RNA, and which when bound by VGAM587 RNA causes inhibition of translation of respective one or more VGAM587 host target proteins.

[25007] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM587 gene, herein designated VGAM GENE, on one or more VGAM587 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25008] It is yet further appreciated that a function of VGAM587 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM587 correlate with, and may be deduced from, the identity of the host target genes which VGAM587 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25009] Nucleotide sequences of the VGAM587 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM587 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM587 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM587 are further described hereinbelow with reference to Table 1.

[25010] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM587 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM587 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25011] As mentioned hereinabove with reference to Fig. 1, a function of VGAM587 gene, herein designated VGAM is inhibition of expression of VGAM587 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM587 correlate with, and may be deduced from, the identity of the target genes which VGAM587 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25012] Desmocollin 3 (DSC3, Accession NM\_001941) is a VGAM587 host target gene. DSC3 BINDING SITE1 and DSC3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DSC3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2

illustrates the complementarity of the nucleotide sequences of DSC3 BINDING SITE1 and DSC3 BINDING SITE2, designated SEQ ID:7652 and SEQ ID:23663 respectively, to the nucleotide sequence of VGAM587 RNA, herein designated VGAM RNA, also designated SEQ ID:3298.

[25013] A function of VGAM587 is therefore inhibition of Desmocollin 3 (DSC3, Accession NM\_001941), a gene which is a component of intercellular desmosome junctions. Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSC3. The function of DSC3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM230. Solute Carrier Family 14 (urea transporter), Member 1 (Kidd blood group) (SLC14A1, Accession NM\_015865) is another VGAM587 host target gene. SLC14A1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SLC14A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC14A1 BINDING SITE, designated SEQ ID:17995, to the nucleotide sequence of VGAM587 RNA,

herein designated VGAM RNA, also designated SEQ ID:3298.

[25014] Another function of VGAM587 is therefore inhibition of Solute Carrier Family 14 (urea transporter), Member 1 (Kidd blood group) (SLC14A1, Accession NM\_015865), a gene which is a urea transporters in spermatogenesis. Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC14A1. The function of SLC14A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM586. Chromosome 8 Open Reading Frame 4 (C8orf4, Accession NM\_020130) is another VGAM587 host target gene. C8orf4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C8orf4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C8orf4 BINDING SITE, designated SEQ ID:21324, to the nucleotide sequence of VGAM587 RNA, herein designated VGAM RNA, also designated SEQ ID:3298.

[25015] Another function of VGAM587 is therefore inhibition of

Chromosome 8 Open Reading Frame 4 (C8orf4, Accession NM\_020130). Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C8orf4. FLJ10700 (Accession NM\_018182) is another VGAM587 host target gene. FLJ10700 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10700 BINDING SITE, designated SEQ ID:20018, to the nucleotide sequence of VGAM587 RNA, herein designated VGAM RNA, also designated SEQ ID:3298.

[25016] Another function of VGAM587 is therefore inhibition of FLJ10700 (Accession NM\_018182). Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10700. FLJ20276 (Accession NM\_017738) is another VGAM587 host target gene. FLJ20276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or



BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20276 BINDING SITE, designated SEQ ID:19326, to the nucleotide sequence of VGAM587 RNA, herein designated VGAM RNA, also designated SEQ ID:3298.

[25017] Another function of VGAM587 is therefore inhibition of FLJ20276 (Accession NM\_017738). Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20276. FLJ21839 (Accession NM\_021831) is another VGAM587 host target gene. FLJ21839 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21839, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21839 BINDING SITE, designated SEQ ID:22405, to the nucleotide sequence of VGAM587 RNA, herein designated VGAM RNA, also designated SEQ ID:3298.

[25018] Another function of VGAM587 is therefore inhibition of FLJ21839 (Accession NM\_021831). Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21839.

LOC163682 (Accession XM\_099402) is another VGAM587 host target gene. LOC163682 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163682, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163682 BINDING SITE, designated SEQ ID:42082, to the nucleotide sequence of VGAM587 RNA, herein designated VGAM RNA, also designated SEQ ID:3298.

[25019] Another function of VGAM587 is therefore inhibition of LOC163682 (Accession XM\_099402). Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163682. LOC169026 (Accession XM\_095471) is another VGAM587 host target gene. LOC169026 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC169026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169026 BINDING SITE, designated SEQ ID:40259, to the nucleotide sequence of VGAM587 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3298.

[25020] Another function of VGAM587 is therefore inhibition of LOC169026 (Accession XM\_095471). Accordingly, utilities of VGAM587 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC169026. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 588 (VGAM588) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25021] VGAM588 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM588 was detected is described hereinabove with reference to Figs. 1–8.

[25022] VGAM588 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM588 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25023] VGAM588 gene encodes a VGAM588 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM588 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM588 precursor RNA is designated SEQ ID:574, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:574 is located at position 41654 relative to the genome of Gallid Herpesvirus 2.

[25024] VGAM588 precursor RNA folds onto itself, forming VGAM588 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25025] An enzyme complex designated DICER COMPLEX, `dices` the VGAM588 folded precursor RNA into VGAM588 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM588 RNA is designated SEQ ID:3299, and is provided hereinbelow with reference to the sequence listing part.

[25026] VGAM588 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM588 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM588 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[25027] VGAM588 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM588 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM588 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM588 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM588 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25028] The complementary binding of VGAM588 RNA, herein designated VGAM RNA, to host target binding sites on VGAM588 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM588 host target RNA into VGAM588 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25029] It is appreciated that VGAM588 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM588 host target genes. The mRNA of

each one of this plurality of VGAM588 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM588 RNA, herein designated VGAM RNA, and which when bound by VGAM588 RNA causes inhibition of translation of respective one or more VGAM588 host target proteins.

[25030] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM588 gene, herein designated VGAM GENE, on one or more VGAM588 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[25031] It is yet further appreciated that a function of VGAM588 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM588 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM588 correlate with, and may be deduced from, the identity of the host target genes which VGAM588 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25032] Nucleotide sequences of the VGAM588 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM588 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM588 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM588 are further described hereinbelow with reference to Table 1.

[25033] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM588 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM588 RNA, herein desig-



nated VGAM RNA, are described hereinbelow with reference to Table 2.

[25034] As mentioned hereinabove with reference to Fig. 1, a function of VGAM588 gene, herein designated VGAM is inhibition of expression of VGAM588 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM588 correlate with, and may be deduced from, the identity of the target genes which VGAM588 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25035] Activating Transcription Factor 5 (ATF5, Accession NM\_012068) is a VGAM588 host target gene. ATF5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATF5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATF5 BINDING SITE, designated SEQ ID:14320, to the nucleotide sequence of VGAM588 RNA, herein designated VGAM RNA, also designated SEQ ID:3299.

[25036] A function of VGAM588 is therefore inhibition of Activating Transcription Factor 5 (ATF5, Accession NM\_012068), a gene which binds to cAMP-inducible promoters and is

involved in gene transcription. Accordingly, utilities of VGAM588 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATF5. The function of ATF5 has been established by previous studies. Using a yeast 2-hybrid screen with CDC34 (OMIM Ref. No. 116948) as the bait, Pati et al. (1999) obtained a partial cDNA encoding ATF5. The deduced 122-amino acid protein contains a C-terminal bZIP motif with only 3 leucines instead of the conventional 5; the 2 distal leucines are replaced by valines. Functional analysis showed that ATF5 is degraded by ubiquitin proteasome machinery in a CDC34- and RAD6B (UBE2B; 179095)-dependent pathway. Using a yeast 2-hybrid screen with PRL1 (PTP4A1; 601585) as the bait, Peters et al. (2001) identified a cDNA encoding ATF5, which they termed ATF7. EMSA analysis indicated that ATF5 binds to CRE but not C/EBP oligonucleotides. Northern blot analysis revealed ubiquitous expression of ATF5, with highest levels in liver, lung, adipose tissue, heart, and skeletal muscle. Coimmunoprecipitation and GST pull-down analyses confirmed the association of the C-terminal bZIP motif of ATF5 with the PTPase domain and adjacent residues of PRL1 in vitro. SDS-PAGE analysis showed that

PRL1 dephosphorylates ATF5.

[25037] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25038] Pati, D.; Meistrich, M. L.; Plon, S. E. : Human Cdc34 and Rad6B ubiquitin–conjugating enzymes target repressors of cyclic AMP–induced transcription for proteolysis. *Molec. Cell. Biol.* 19: 5001–5013, 1999. ; and

[25039] Peters, C. S.; Liang, X.; Li, S.; Kannan, S.; Peng, Y.; Taub, R.; Diamond, R. H. : ATF–7, a novel bZIP protein, interacts with the PRL–1 protein–tyrosine phosphatase. *J. Biol. Chem.* 276.

[25040] Further studies establishing the function and utilities of ATF5 are found in John Hopkins OMIM database record ID 606398, and in cited publications numbered 451 and 4523–4524 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FK506 Binding Protein 9, 63 KDa (FKBP9, Accession XM\_168403) is another VGAM588 host target gene. FKBP9 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FKBP9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus–

trates the complementarity of the nucleotide sequences of FKBP9 BINDING SITE, designated SEQ ID:45144, to the nucleotide sequence of VGAM588 RNA, herein designated VGAM RNA, also designated SEQ ID:3299.

[25041] Another function of VGAM588 is therefore inhibition of FK506 Binding Protein 9, 63 KDa (FKBP9, Accession XM\_168403). Accordingly, utilities of VGAM588 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FKBP9. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 589 (VGAM589) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25042] VGAM589 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM589 was detected is described hereinabove with reference to Figs. 1–8.

[25043] VGAM589 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM589 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[25044] VGAM589 gene encodes a VGAM589 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM589 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM589 precursor RNA is designated SEQ ID:575, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:575 is located at position 37271 relative to the genome of Gallid Herpesvirus 2.

[25045] VGAM589 precursor RNA folds onto itself, forming VGAM589 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25046] An enzyme complex designated DICER COMPLEX, `dices` the VGAM589 folded precursor RNA into VGAM589 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 70%) nucleotide sequence of VGAM589 RNA is designated SEQ ID:3300, and is provided hereinbelow with reference to the sequence listing part.

[25047] VGAM589 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM589 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM589 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25048] VGAM589 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM589 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM589 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM589 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM589 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25049] The complementary binding of VGAM589 RNA, herein designated VGAM RNA, to host target binding sites on VGAM589 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM589 host target RNA into VGAM589 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25050] It is appreciated that VGAM589 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM589 host target genes. The mRNA of each one of this plurality of VGAM589 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM589 RNA, herein designated VGAM RNA, and which when bound by VGAM589 RNA causes inhibition of translation of respective one or more VGAM589 host target proteins.

[25051] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM589 gene, herein designated VGAM GENE, on one or more VGAM589 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-



though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25052] It is yet further appreciated that a function of VGAM589 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM589 correlate with, and may be deduced from, the identity of the host target genes which VGAM589 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25053] Nucleotide sequences of the VGAM589 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM589 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM589 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM589 are further described hereinbelow with reference to Table 1.

[25054] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM589 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM589 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25055] As mentioned hereinabove with reference to Fig. 1, a function of VGAM589 gene, herein designated VGAM is inhibition of expression of VGAM589 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM589 correlate with, and may be deduced from, the identity of the target genes which VGAM589 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25056] B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993) is a VGAM589 host target gene. BCL7A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL7A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL7A BINDING SITE, designated SEQ ID:21994, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25057] A function of VGAM589 is therefore inhibition of B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL7A. Deoxyguanosine Kinase (DGUOK, Accession NM\_080915) is another VGAM589 host target gene. DGUOK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DGUOK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGUOK BINDING SITE, designated SEQ ID:28135, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25058] Another function of VGAM589 is therefore inhibition of Deoxyguanosine Kinase (DGUOK, Accession NM\_080915), a gene which is deoxyguanosine kinase and mediates phosphorylation of several deoxyribonucleosides. Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DGUOK. The function of DGUOK and its association with various diseases and clinical conditions, has

been established by previous studies, as described herein above with reference to VGAM121. Down Syndrome Critical Region Gene 1 (DSCR1, Accession NM\_004414) is another VGAM589 host target gene. DSCR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DSCR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DSCR1 BINDING SITE, designated SEQ ID:10675, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25059] Another function of VGAM589 is therefore inhibition of Down Syndrome Critical Region Gene 1 (DSCR1, Accession NM\_004414), a gene which inhibits calcineurin-dependent transcriptional responses. Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSCR1. The function of DSCR1 has been established by previous studies. The study of patients with partial trisomy 21 has defined an area of approximately 3 Mb at chromosomal region 21q22 as the minimal candidate region for the Down syndrome phenotype (OMIM Ref. No. 190685). Us-

ing a novel exon cloning strategy, Fuentes et al. (1995) identified several putative exons from region 21q22.1–q22.2. One exon was used to isolate fetal brain cDNAs corresponding to a gene that the authors designated DSCR1. The predicted 171–amino acid protein contains 2 proline–rich regions, a putative DNA–binding domain, and an acidic region. Northern blot analysis revealed that the 2.2–kb DSCR1 transcript is expressed at the highest levels in fetal brain and adult heart and at lower levels in various other tissues. An additional 2–kb mRNA was detected in fetal and adult liver. Increased expression in the brains of young rats compared with adults suggested to Fuentes et al. (1995) that DSCR1 plays a role during central nervous system development. Fuentes et al. (1997) determined that DSCR1 spans nearly 45 kb and contains 7 exons, 4 of which are alternative first exons. They found tissue–specific expression patterns for the alternative transcripts. Kingsbury and Cunningham (2000) referred to the proteins encoded by the MCIP genes as calciopressins. Functional analysis showed that when expressed in yeast, DSCR1 and ZAKI4 inhibited calcineurin function. The authors proposed that increased expression of DSCR1 in trisomy–21 individuals may contribute to the

neurologic, cardiac, or immunologic defects of Down syndrome.

[25060] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25061] Fuentes, J. J.; Pritchard, M. A.; Estivill, X. : Genomic organization, alternative splicing, and expression patterns of the DSCR1 (Down syndrome candidate region 1) gene. *Genomics* 44: 358–361, 1997. ; and

[25062] Kingsbury, T. J.; Cunningham, K. W. : A conserved family of calcineurin regulators. *Genes Dev.* 14: 1595–1604, 2000.

[25063] Further studies establishing the function and utilities of DSCR1 are found in John Hopkins OMIM database record ID 602917, and in cited publications numbered 6049, 6192–619 and 5335–5336 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Interleukin 2 Receptor, Beta (IL2RB, Accession NM\_000878) is another VGAM589 host target gene. IL2RB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL2RB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of IL2RB BINDING SITE, designated SEQ ID:6575, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25064] Another function of VGAM589 is therefore inhibition of Interleukin 2 Receptor, Beta (IL2RB, Accession NM\_000878), a gene which is involved in receptor mediated endocytosis and transduces the mitogenic signals of il-2. Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL2RB. The function of IL2RB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM450. Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), Beta Polypeptide (protein disulfide isomerase; thyroid hormone binding protein p55) (P4HB, Accession NM\_000918) is another VGAM589 host target gene. P4HB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P4HB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of P4HB BINDING SITE, designated SEQ ID:6628, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25065] Another function of VGAM589 is therefore inhibition of Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), Beta Polypeptide (protein disulfide isomerase; thyroid hormone binding protein p55) (P4HB, Accession NM\_000918), a gene which catalyzes formation of 4-hydroxyproline in collagens. Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P4HB. The function of P4HB has been established by previous studies. Prolyl 4-hydroxylase (EC 1.14.11.2) is involved in hydroxylation of prolyl residues in procollagen. Pihlajaniemi et al. (1987) cloned the PROHB gene. Prolyl 4-hydroxylase is a tetramer consisting of 2 alpha (176710, 600608) and 2 beta subunits of molecular weights about 64,000 and 60,000, respectively, for the monomers. Characterization of cDNA clones for the human beta subunit indicated that the polypeptide is 508 amino acids long, including a signal peptide of 17 amino acids. Pihlajaniemi et al. (1987) also found that disulfide



isomerase (EC 5.3.4.1) is a product of the same gene. When present in cells in monomeric form, the protein serves the function of DSI (Koivu et al., 1987); when present in the prolyl 4-hydroxylase tetramer, it catalyzes the formation of 4-hydroxyproline in collagen. Cheng et al. (1987) demonstrated by molecular cloning and nucleotide sequencing that cellular thyroid hormone-binding protein is also identical to the beta subunit of prolyl 4-hydroxylase and protein disulfide isomerase. Tasanen et al. (1988) isolated genomic clones for the human gene coding for this multifunctional protein. They found that the gene is about 18 kb long and consists of 11 exons. The codons for the 2 presumed active sites of protein disulfide isomerase, each a cys-gly-his-cys sequence, were found to be located 12 bp from the beginning of exons 2 and 9. Another of the many functions of protein disulfide isomerase is its role as the smaller element of the heterodimeric microsomal triglyceride transfer protein (MTP; 157147). The unique larger subunit of this heterodimer is mutant in patients with abetalipoproteinemia (OMIM Ref. No. 200100). Since chylomicrons, very low density lipoproteins, and low density lipoproteins are absent from the plasma in abetalipoproteinemic subjects,

and since the clinical pathology of abetalipoproteinemia results from deficiency of fat-soluble vitamins that are transported on apoB-containing lipoproteins, Sharp et al. (1993) proposed that inhibition of MTP may provide a specific mechanism for lowering plasma cholesterol and triglyceride levels.

[25066] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25067] Pihlajaniemi, T.; Helaakoski, T.; Tasanen, K.; Myllyla, R.; Huhtala, M.-L.; Koivu, J.; Kivirikko, K. I. : Molecular cloning of the beta-subunit of human prolyl 4-hydroxylase: this subunit and protein disulphide isomerase are products of the same gene. EMBO J. 6: 643-649, 1987. ; and

[25068] Sharp, D.; Blinderman, L.; Combs, K. A.; Kienzle, B.; Ricci, B.; Wager-Smith, K.; Gil, C. M.; Turck, C. W.; Bouma, M.-E.; Rader, D. J.; Aggerbeck, L. P.; Gregg, R. E.; Gordon, D. A.; We.

[25069] Further studies establishing the function and utilities of P4HB are found in John Hopkins OMIM database record ID 176790, and in cited publications numbered 9725-9734, 329 and 9735 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer-

ence.poly(A)-specific Ribonuclease (deadenylation nuclease) (PARN, Accession NM\_002582) is another VGAM589 host target gene. PARN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PARN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PARN BINDING SITE, designated SEQ ID:8444, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25070] Another function of VGAM589 is therefore inhibition of poly(A)-specific Ribonuclease (deadenylation nuclease) (PARN, Accession NM\_002582), a gene which degrades mRNA poly(A) tails during oocyte maturation. Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PARN. The function of PARN has been established by previous studies. Exonucleolytic degradation of the poly(A) tail is often the first step in the decay of eukaryotic mRNAs. Korner and Wahle (1997) purified the enzyme for deadenylation, PARN, which they named DAN, from calf thymus. Korner et al. (1998) partially sequenced the

bovine PARN protein. By searching an EST database with the bovine PARN peptide sequences, they identified a human PARN EST encoding a deduced 639-amino acid protein. The calculated molecular mass of human PARN is 73.5 kD, which was the mass of recombinant PARN expressed in *E. coli*. The human PARN protein shows sequence similarity to the RNase D family of 3-prime exonucleases, which includes *E. coli* polymerase I. PARN is a 3-prime exonuclease that prefers poly(A) as the substrate. In an in vitro assay, PARN activity was partially inhibited by PAB1 (OMIM Ref. No. 604679), resulting in phased shortening of the poly(A) tail of the polyadenylated RNA substrate. The PARN protein is located in both the nucleus and the cytoplasm. It is not stably associated with polysomes or ribosomal subunits. Northern blot analysis detected a 3.1-kb PARN transcript in HeLa cell extracts. The authors noted that the PARN gene is widely expressed. Korner et al. (1998) noted that the PARN gene maps to chromosome 16.

[25071] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25072] Korner, C. G.; Wahle, E. : Poly(A) tail shortening by a

mammalian poly(A)-specific 3-prime-exoribonuclease. J. Biol. Chem. 272: 10448-10456, 1997. ; and

[25073] Korner, C. G.; Wormington, M.; Muckenthaler, M.; Schneider, S.; Dehlin, E.; Wahle, E. : The deadenylating nuclease (DAN) is involved in poly(A) tail removal during the meiotic maturation.

[25074] Further studies establishing the function and utilities of PARN are found in John Hopkins OMIM database record ID 604212, and in cited publications numbered 4921-4922 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphoribosyl Pyrophosphate Amidotransferase (PPAT, Accession NM\_002703) is another VGAM589 host target gene. PPAT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPAT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPAT BINDING SITE, designated SEQ ID:8551, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25075] Another function of VGAM589 is therefore inhibition of Phosphoribosyl Pyrophosphate Amidotransferase (PPAT,

Accession NM\_002703). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPAT. Alpha 1,4-galactosyltransferase (A4GALT, Accession NM\_017436) is another VGAM589 host target gene. A4GALT BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by A4GALT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of A4GALT BINDING SITE, designated SEQ ID:18896, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25076] Another function of VGAM589 is therefore inhibition of Alpha 1,4-galactosyltransferase (A4GALT, Accession NM\_017436). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with A4GALT. FLJ20309 (Accession NM\_017759) is another VGAM589 host target gene. FLJ20309 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20309, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20309 BINDING SITE, designated SEQ ID:19371, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25077] Another function of VGAM589 is therefore inhibition of FLJ20309 (Accession NM\_017759). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20309. FLJ21916 (Accession NM\_023112) is another VGAM589 host target gene. FLJ21916 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21916, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21916 BINDING SITE, designated SEQ ID:23384, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25078] Another function of VGAM589 is therefore inhibition of FLJ21916 (Accession NM\_023112). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ21916. KIAA1089 (Accession XM\_044148) is another VGAM589 host target gene. KIAA1089 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1089, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1089 BINDING SITE, designated SEQ ID:34142, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25079] Another function of VGAM589 is therefore inhibition of KIAA1089 (Accession XM\_044148). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1089. KIAA1538 (Accession XM\_049474) is another VGAM589 host target gene. KIAA1538 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1538 BINDING SITE, designated SEQ ID:35433, to the



nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25080] Another function of VGAM589 is therefore inhibition of KIAA1538 (Accession XM\_049474). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1538. Sideroflexin 5 (SFXN5, Accession NM\_144579) is another VGAM589 host target gene. SFXN5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFXN5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFXN5 BINDING SITE, designated SEQ ID:29389, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25081] Another function of VGAM589 is therefore inhibition of Sideroflexin 5 (SFXN5, Accession NM\_144579). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFXN5. WD Repeat Domain 13 (WDR13, Accession NM\_017883) is another VGAM589 host target gene. WDR13 BINDING SITE is HOST TARGET binding site found

in the 5' untranslated region of mRNA encoded by WDR13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WDR13 BINDING SITE, designated SEQ ID:19552, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25082] Another function of VGAM589 is therefore inhibition of WD Repeat Domain 13 (WDR13, Accession NM\_017883). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WDR13. LOC124997 (Accession XM\_058886) is another VGAM589 host target gene. LOC124997 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC124997, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124997 BINDING SITE, designated SEQ ID:36787, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25083] Another function of VGAM589 is therefore inhibition of LOC124997 (Accession XM\_058886). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124997. LOC150174 (Accession XM\_086802) is another VGAM589 host target gene. LOC150174 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150174, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150174 BINDING SITE, designated SEQ ID:38875, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25084] Another function of VGAM589 is therefore inhibition of LOC150174 (Accession XM\_086802). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150174. LOC150213 (Accession XM\_059324) is another VGAM589 host target gene. LOC150213 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150213, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150213 BINDING SITE, designated SEQ ID:36962, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25085] Another function of VGAM589 is therefore inhibition of LOC150213 (Accession XM\_059324). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150213. LOC150236 (Accession XM\_086824) is another VGAM589 host target gene. LOC150236 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150236, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150236 BINDING SITE, designated SEQ ID:38907, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25086] Another function of VGAM589 is therefore inhibition of LOC150236 (Accession XM\_086824). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC150236. LOC153218 (Accession XM\_087628) is another VGAM589 host target gene. LOC153218 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC153218, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153218 BINDING SITE, designated SEQ ID:39365, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25087] Another function of VGAM589 is therefore inhibition of LOC153218 (Accession XM\_087628). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153218. LOC154525 (Accession XM\_098554) is another VGAM589 host target gene. LOC154525 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154525 BINDING SITE, designated SEQ ID:41708, to the nucleotide sequence of VGAM589 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3300.

[25088] Another function of VGAM589 is therefore inhibition of LOC154525 (Accession XM\_098554). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154525. LOC200261 (Accession XM\_114172) is another VGAM589 host target gene. LOC200261 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200261 BINDING SITE, designated SEQ ID:42751, to the nucleotide sequence of VGAM589 RNA, herein designated VGAM RNA, also designated SEQ ID:3300.

[25089] Another function of VGAM589 is therefore inhibition of LOC200261 (Accession XM\_114172). Accordingly, utilities of VGAM589 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200261. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 590 (VGAM590) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25090] VGAM590 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM590 was detected is described hereinabove with reference to Figs. 1–8.

[25091] VGAM590 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM590 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25092] VGAM590 gene encodes a VGAM590 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM590 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM590 precursor RNA is designated SEQ ID:576, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:576 is located at position 37055 relative to the genome of Gallid Herpesvirus 2.

[25093] VGAM590 precursor RNA folds onto itself, forming

VGAM590 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25094] An enzyme complex designated DICER COMPLEX, `dices` the VGAM590 folded precursor RNA into VGAM590 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 55%) nucleotide sequence of VGAM590 RNA is designated SEQ ID:3301, and is provided hereinbelow with reference to the sequence listing part.

[25095] VGAM590 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM590 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM590 host target RNA comprises



three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[25096] VGAM590 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM590 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM590 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM590 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM590 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25097] The complementary binding of VGAM590 RNA, herein designated VGAM RNA, to host target binding sites on VGAM590 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM590 host target RNA into VGAM590 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25098] It is appreciated that VGAM590 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM590 host target genes. The mRNA of each one of this plurality of VGAM590 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM590 RNA, herein designated VGAM RNA, and which when bound by VGAM590 RNA causes inhibition of translation of respective one or more VGAM590 host target proteins.

[25099] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM590 gene, herein designated VGAM GENE, on one or more VGAM590 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25100] It is yet further appreciated that a function of VGAM590 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM590 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM590 correlate with, and may be deduced from, the identity of the host target genes which VGAM590 binds and inhibits, and

the function of these host target genes, as elaborated hereinbelow.

[25101] Nucleotide sequences of the VGAM590 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM590 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM590 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM590 are further described hereinbelow with reference to Table 1.

[25102] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM590 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM590 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25103] As mentioned hereinabove with reference to Fig. 1, a function of VGAM590 gene, herein designated VGAM is inhibition of expression of VGAM590 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM590 correlate with, and may be deduced from, the identity of the target genes which VGAM590 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[25104] Translin (TSN, Accession NM\_004622) is a VGAM590 host target gene. TSN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSN BINDING SITE, designated SEQ ID:10982, to the nucleotide sequence of VGAM590 RNA, herein designated VGAM RNA, also designated SEQ ID:3301.

[25105] A function of VGAM590 is therefore inhibition of Translin (TSN, Accession NM\_004622), a gene which is a DNA binding protein and involved in DNA repair, replication, or recombination. Accordingly, utilities of VGAM590 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSN. The function of TSN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM98.KIAA0318 (Accession XM\_044334) is another VGAM590 host target gene. KIAA0318 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by KIAA0318, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0318 BINDING SITE, designated SEQ ID:34184, to the nucleotide sequence of VGAM590 RNA, herein designated VGAM RNA, also designated SEQ ID:3301.

[25106] Another function of VGAM590 is therefore inhibition of KIAA0318 (Accession XM\_044334). Accordingly, utilities of VGAM590 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0318. LOC142779 (Accession XM\_084337) is another VGAM590 host target gene. LOC142779 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC142779, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC142779 BINDING SITE, designated SEQ ID:37558, to the nucleotide sequence of VGAM590 RNA, herein designated VGAM RNA, also designated SEQ ID:3301.

[25107] Another function of VGAM590 is therefore inhibition of LOC142779 (Accession XM\_084337). Accordingly, utilities

of VGAM590 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC142779. LOC200609 (Accession XM\_117256) is another VGAM590 host target gene. LOC200609 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200609, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200609 BINDING SITE, designated SEQ ID:43323, to the nucleotide sequence of VGAM590 RNA, herein designated VGAM RNA, also designated SEQ ID:3301.

[25108] Another function of VGAM590 is therefore inhibition of LOC200609 (Accession XM\_117256). Accordingly, utilities of VGAM590 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200609. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 591 (VGAM591) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25109] VGAM591 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM591 was detected is described hereinabove with reference to Figs. 1–8.

[25110] VGAM591 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM591 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25111] VGAM591 gene encodes a VGAM591 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM591 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM591 precursor RNA is designated SEQ ID:577, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:577 is located at position 47365 relative to the genome of Gallid Herpesvirus 2.

[25112] VGAM591 precursor RNA folds onto itself, forming VGAM591 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this



`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25113] An enzyme complex designated DICER COMPLEX, `dices` the VGAM591 folded precursor RNA into VGAM591 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM591 RNA is designated SEQ ID:3302, and is provided hereinbelow with reference to the sequence listing part.

[25114] VGAM591 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM591 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM591 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[25115] VGAM591 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM591 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM591 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM591 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM591 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25116] The complementary binding of VGAM591 RNA, herein designated VGAM RNA, to host target binding sites on VGAM591 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM591 host target RNA into VGAM591 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25117] It is appreciated that VGAM591 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM591 host target genes. The mRNA of each one of this plurality of VGAM591 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM591 RNA, herein designated VGAM RNA, and which when bound by VGAM591 RNA causes inhibition of translation of respective one or more VGAM591 host target proteins.

[25118] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM591 gene, herein designated VGAM GENE, on one or more VGAM591 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25119] It is yet further appreciated that a function of VGAM591 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM591 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM591 correlate with, and may be deduced from, the identity of the host target genes which VGAM591 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25120] Nucleotide sequences of the VGAM591 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM591 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM591 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM591 are further  
described hereinbelow with reference to Table 1.

[25121] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM591 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM591 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[25122] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM591 gene, herein designated VGAM is  
inhibition of expression of VGAM591 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM591 correlate with, and may be deduced  
from, the identity of the target genes which VGAM591  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[25123] LOC153196 (Accession XM\_098323) is a VGAM591 host  
target gene. LOC153196 BINDING SITE is HOST TARGET

binding site found in the 5` untranslated region of mRNA encoded by LOC153196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153196 BINDING SITE, designated SEQ ID:41593, to the nucleotide sequence of VGAM591 RNA, herein designated VGAM RNA, also designated SEQ ID:3302.

[25124] A function of VGAM591 is therefore inhibition of LOC153196 (Accession XM\_098323). Accordingly, utilities of VGAM591 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153196. LOC158014 (Accession XM\_088442) is another VGAM591 host target gene. LOC158014 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC158014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158014 BINDING SITE, designated SEQ ID:39690, to the nucleotide sequence of VGAM591 RNA, herein designated VGAM RNA, also designated SEQ ID:3302.

[25125] Another function of VGAM591 is therefore inhibition of

LOC158014 (Accession XM\_088442). Accordingly, utilities of VGAM591 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158014. LOC158318 (Accession XM\_098925) is another VGAM591 host target gene. LOC158318 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158318, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158318 BINDING SITE, designated SEQ ID:41959, to the nucleotide sequence of VGAM591 RNA, herein designated VGAM RNA, also designated SEQ ID:3302.

[25126] Another function of VGAM591 is therefore inhibition of LOC158318 (Accession XM\_098925). Accordingly, utilities of VGAM591 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158318. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 592 (VGAM592) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[25127] VGAM592 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM592 was detected is described hereinabove with reference to Figs. 1–8.

[25128] VGAM592 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM592 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25129] VGAM592 gene encodes a VGAM592 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM592 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM592 precursor RNA is designated SEQ ID:578, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:578 is located at position 44626 relative to the genome of Gallid Herpesvirus 2.

[25130] VGAM592 precursor RNA folds onto itself, forming VGAM592 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional



`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[25131] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM592 folded precursor RNA into VGAM592 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 44%) nucleotide se-  
quence of VGAM592 RNA is designated SEQ ID:3303, and  
is provided hereinbelow with reference to the sequence  
listing part.

[25132] VGAM592 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM592 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM592 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[25133] VGAM592 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM592 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM592 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM592 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM592 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[25134] The complementary binding of VGAM592 RNA, herein designated VGAM RNA, to host target binding sites on VGAM592 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM592 host target RNA into VGAM592 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25135] It is appreciated that VGAM592 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM592 host target genes. The mRNA of each one of this plurality of VGAM592 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM592 RNA, herein designated VGAM RNA, and which when bound by VGAM592 RNA causes inhibition of translation of respective one or more VGAM592 host target proteins.

[25136] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM592 gene, herein designated VGAM GENE, on one or

more VGAM592 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25137] It is yet further appreciated that a function of VGAM592 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM592 correlate with, and may be deduced from, the identity of the host target genes which VGAM592 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [25138] Nucleotide sequences of the VGAM592 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM592 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM592 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM592 are further described hereinbelow with reference to Table 1.
- [25139] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM592 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM592 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [25140] As mentioned hereinabove with reference to Fig. 1, a function of VGAM592 gene, herein designated VGAM is inhibition of expression of VGAM592 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM592 correlate with, and may be deduced from, the identity of the target genes which VGAM592 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [25141] BN51 (BHK21) Temperature Sensitivity Complementing

(BN51T, Accession XM\_113557) is a VGAM592 host target gene. BN51T BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BN51T, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BN51T BINDING SITE, designated SEQ ID:42284, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25142] A function of VGAM592 is therefore inhibition of BN51 (BHK21) Temperature Sensitivity Complementing (BN51T, Accession XM\_113557), a gene which complements a temperature-sensitive cell cycle mutation in BHK cells. Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BN51T. The function of BN51T has been established by previous studies. Two temperature-sensitive mutants have been isolated from the BHK-21 Syrian hamster cell line. Both of the human genes that complement these mutations, designated ts11 and tsBN51, lead to a block in progression through the G1 phase of the cell cycle at nonpermissive temperatures. Ts11 has been identi-

fied as asparagine synthetase; see 108370. The tsBN51 gene encodes a highly charged novel protein of 395 amino acids (Ittmann et al., 1987) whose biochemical function had not yet been determined when Greco et al. (1989) assigned the gene to 8q21 by study of rodent-human hybrid cells and by in situ hybridization using a tsBN51 probe. This is one of a considerable number of temperature-sensitive mutants which have been mapped to various autosomes and in several instances to the X chromosome.

[25143] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25144] Ittmann, M.; Greco, A.; Basilico, C. : Isolation of the human gene that complements a temperature-sensitive cell cycle mutation in BHK cells. *Molec. Cell. Biol.* 7: 3386-3393, 1987. ; and

[25145] Greco, A.; Ittmann, M.; Barletta, C.; Basilico, C.; Croce, C. M.; Cannizzaro, L. A.; Huebner, K. : Chromosomal localization of human genes required for G(1) progression in mammalian cell.

[25146] Further studies establishing the function and utilities of BN51T are found in John Hopkins OMIM database record

ID 187280, and in cited publications numbered 12373–12374 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cyclin-dependent Kinase Inhibitor 1B (p27, Kip1) (CDKN1B, Accession NM\_004064) is another VGAM592 host target gene. CDKN1B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDKN1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDKN1B BINDING SITE, designated SEQ ID:10274, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25147] Another function of VGAM592 is therefore inhibition of Cyclin-dependent Kinase Inhibitor 1B (p27, Kip1) (CDKN1B, Accession NM\_004064), a gene which is involved in g1 arrest and may mediate tgfbeta-induced g1 arrest. Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDKN1B. The function of CDKN1B has been established by previous studies. Stegmaier et al. (1995) studied loss of heterozygosity (LOH) in the region



12p13–p12 in acute lymphoblastic leukemia; this chromosomal region often shows deletion in such patients. In 15% of informative patients, there was evidence of LOH of the TEL locus (OMIM Ref. No. 600618) which was not evident on cytogenetic analysis. Detailed examination of patients with LOH showed that the critically deleted region included a second candidate tumor suppressor gene, referred to by them as KIP1, which encodes the cyclin-dependent kinase inhibitor previously called p27 (Toyoshima and Hunter, 1994 and Polyak et al., 1994). Based on the STS content of TEL-positive YACs, Stegmaier et al. (1995) reported that KIP1 and TEL were in close proximity. Apoptosis of human endothelial cells after growth factor deprivation is associated with rapid and dramatic upregulation of cyclin A-associated CDK2 activity. Levkau et al. (1998) showed that in apoptotic cells the carboxyl-termini of the CDK inhibitors CDKN1A (OMIM Ref. No. 116899) and CDKN1B are truncated by specific cleavage. The enzyme involved in this cleavage is CASP3 (OMIM Ref. No. 600636) and/or a CASP3-like caspase. After cleavage, CDKN1A loses its nuclear localization sequence and exits the nucleus. Cleavage of CDKN1A and CDKN1B resulted in a substantial reduction in their asso-

ciation with nuclear cyclin-CDK2 complexes, leading to a dramatic induction of CDK2 activity. Dominant-negative CDK2, as well as a mutant CDKN1A resistant to caspase cleavage, partially suppressed apoptosis. These data suggested that CDK2 activation, through caspase-mediated cleavage of CDK inhibitors, may be instrumental in the execution of apoptosis following caspase activation.

[25148] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25149] Levkau, B.; Koyama, H.; Raines, E. W.; Clurman, B. E.; Herren, B.; Orth, K.; Roberts, J. M.; Ross, R. : Cleavage of p21(Cip1/Waf1) and p27(Kip1) mediates apoptosis in endothelial cells through activation of Cdk2: role of a caspase cascade. *Molec. Cell* 1: 553-563, 1998. ; and

[25150] Stegmaier, K.; Pendse, S.; Barker, G. F.; Bray-Ward, P.; Ward, D. C.; Montgomery, K. T.; Krauter, K. S.; Reynolds, C.; Sklar, J.; Donnelly, M.; Bohlander, S. K.; Rowley, J. D.; Sallan.

[25151] Further studies establishing the function and utilities of CDKN1B are found in John Hopkins OMIM database record ID 600778, and in cited publications numbered 5665, 9927-9930, 7124, 9936-9937, 12194, 9939-9940,

4705, 994 and 9942 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Laminin, Gamma 2 (LAMC2, Accession NM\_005562) is another VGAM592 host target gene. LAMC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LAMC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LAMC2 BINDING SITE, designated SEQ ID:12090, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25152] Another function of VGAM592 is therefore inhibition of Laminin, Gamma 2 (LAMC2, Accession NM\_005562). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LAMC2. PAG (Accession NM\_018440) is another VGAM592 host target gene. PAG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAG BINDING

SITE, designated SEQ ID:20512, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25153] Another function of VGAM592 is therefore inhibition of PAG (Accession NM\_018440). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAG. Retinoblastoma-like 1 (p107) (RBL1, Accession NM\_002895) is another VGAM592 host target gene. RBL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RBL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RBL1 BINDING SITE, designated SEQ ID:8802, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25154] Another function of VGAM592 is therefore inhibition of Retinoblastoma-like 1 (p107) (RBL1, Accession NM\_002895), a gene which has an important role in negatively regulating the rate of progression of the cell cycle. Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with RBL1. The function of RBL1 has been established by previous studies. The cellular protein p107, like the retinoblastoma gene product (OMIM Ref. No. 180200), has been shown to form a specific complex with adenovirus E1A and SV40 large T antigen (T). The binding characteristics implied that RB1 and p107 share a common biochemical function. Ewen et al. (1991) used a partial cDNA for human p107 to map the gene to 20q11.2 by fluorescence in situ hybridization. The cDNA encoded a 936-residue protein. Comparison with RB1 showed a major region of homology extending over 564 residues. This region in RB1 is essential to its growth-controlling function. Sequences outside of this region are largely unique to each protein. Animal model experiments lend further support to the function of RBL1. LeCouter et al. (1998) introduced a null mutation in p107 into the germ line of mice and bred into a BALB/cJ genetic background. Mice lacking p107 were viable and fertile but displayed impaired growth, reaching about 50% of normal weight by 21 days of age. Mutant mice exhibited a myeloproliferative disorder characterized by ectopic myeloid hyperplasia in the spleen and liver. Embryonic p107  $-/-$  fibroblasts and primary myoblasts isolated from adult p107  $-/-$  mice

displayed a striking 2-fold acceleration in doubling time. However, cell sort analysis indicated that the fraction of cells in G1, S, and G2 was unaltered, suggesting that the different phases of the cell cycle in p107  $-/-$  cells was uniformly reduced by a factor of 2. Western analysis of cyclin expression in synchronized p107  $-/-$  fibroblasts revealed that expression of cyclins E and A preceded that of D1. Mutant embryos expressed approximately twice the normal levels of Rb, whereas p130 levels were unaltered. Finally, mutant mice reverted to a wildtype phenotype following a single backcross with C57BL/6J mice, suggesting the existence of modifier genes that have potentially epistatic relationships with p107. LeCouter et al. (1998) concluded that p107 has an important role in negatively regulating the rate of progression of the cell cycle, but in a strain-dependent manner.

[25155] It is appreciated that the abovementioned animal model for RBL1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[25156] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [25157] Ewen, M. E.; Xing, Y.; Lawrence, J. B.; Livingston, D. M. : Molecular cloning, chromosomal mapping, and expression of the cDNA for p107, a retinoblastoma gene product-related protein. Cell 66: 1155–1164, 1991. ; and
- [25158] LeCouter, J. E.; Kablar, B.; Hardy, W. R.; Ying, C.; Megeney, L. A.; May, L. L.; Rudnicki, M. A. : Strain-dependent myeloid hyperplasia, growth deficiency, and accelerated cell cycle in.
- [25159] Further studies establishing the function and utilities of RBL1 are found in John Hopkins OMIM database record ID 116957, and in cited publications numbered 12349–4450 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Suppressor of Cytokine Signaling 5 (SOCS5, Accession NM\_014011) is another VGAM592 host target gene. SOCS5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SOCS5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOCS5 BINDING SITE, designated SEQ ID:15228, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25160] Another function of VGAM592 is therefore inhibition of Suppressor of Cytokine Signaling 5 (SOCS5, Accession NM\_014011). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOCS5. FLJ23017 (Accession NM\_022840) is another VGAM592 host target gene. FLJ23017 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23017 BINDING SITE, designated SEQ ID:23130, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25161] Another function of VGAM592 is therefore inhibition of FLJ23017 (Accession NM\_022840). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23017. KIAA0354 (Accession NM\_014872) is another VGAM592 host target gene. KIAA0354 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0354, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0354 BINDING SITE, designated SEQ ID:16997, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25162] Another function of VGAM592 is therefore inhibition of KIAA0354 (Accession NM\_014872). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0354. KIAA0472 (Accession XM\_050147) is another VGAM592 host target gene. KIAA0472 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0472, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0472 BINDING SITE, designated SEQ ID:35579, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25163] Another function of VGAM592 is therefore inhibition of KIAA0472 (Accession XM\_050147). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0472. KIAA1297 (Accession XM\_051005) is another VGAM592 host target gene. KIAA1297 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1297, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1297 BINDING SITE, designated SEQ ID:35718, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25164] Another function of VGAM592 is therefore inhibition of KIAA1297 (Accession XM\_051005). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1297. l(3)mbt-like 2 (Drosophila) (L3MBTL2, Accession XM\_114201) is another VGAM592 host target gene. L3MBTL2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by L3MBTL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of L3MBTL2 BINDING SITE, designated SEQ

ID:42793, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25165] Another function of VGAM592 is therefore inhibition of I(3)mbt-like 2 (Drosophila) (L3MBTL2, Accession XM\_114201). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with L3MBTL2. LEC3 (Accession NM\_015236) is another VGAM592 host target gene. LEC3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LEC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LEC3 BINDING SITE, designated SEQ ID:17572, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25166] Another function of VGAM592 is therefore inhibition of LEC3 (Accession NM\_015236). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LEC3. TUSP (Accession NM\_020245) is another VGAM592 host target gene. TUSP BINDING SITE is HOST TARGET binding

site found in the 3` untranslated region of mRNA encoded by TUSP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TUSP BINDING SITE, designated SEQ ID:21532, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25167] Another function of VGAM592 is therefore inhibition of TUSP (Accession NM\_020245). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TUSP. LOC143308 (Accession XM\_096411) is another VGAM592 host target gene. LOC143308 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC143308, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143308 BINDING SITE, designated SEQ ID:40349, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25168] Another function of VGAM592 is therefore inhibition of

LOC143308 (Accession XM\_096411). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143308. LOC146136 (Accession XM\_053737) is another VGAM592 host target gene. LOC146136 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146136, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146136 BINDING SITE, designated SEQ ID:36111, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25169] Another function of VGAM592 is therefore inhibition of LOC146136 (Accession XM\_053737). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146136. LOC150225 (Accession XM\_097870) is another VGAM592 host target gene. LOC150225 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150225, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC150225 BINDING SITE, designated SEQ ID:41190, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25170] Another function of VGAM592 is therefore inhibition of LOC150225 (Accession XM\_097870). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150225. LOC152860 (Accession XM\_087539) is another VGAM592 host target gene. LOC152860 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152860, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152860 BINDING SITE, designated SEQ ID:39325, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25171] Another function of VGAM592 is therefore inhibition of LOC152860 (Accession XM\_087539). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152860. LOC158301 (Accession XM\_088543) is an-

other VGAM592 host target gene. LOC158301 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC158301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158301 BINDING SITE, designated SEQ ID:39810, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25172] Another function of VGAM592 is therefore inhibition of LOC158301 (Accession XM\_088543). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158301. LOC220565 (Accession XM\_165417) is another VGAM592 host target gene. LOC220565 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC220565, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220565 BINDING SITE, designated SEQ ID:43635, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25173] Another function of VGAM592 is therefore inhibition of LOC220565 (Accession XM\_165417). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220565. LOC221810 (Accession XM\_168222) is another VGAM592 host target gene. LOC221810 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221810, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221810 BINDING SITE, designated SEQ ID:45085, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25174] Another function of VGAM592 is therefore inhibition of LOC221810 (Accession XM\_168222). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221810. LOC255158 (Accession XM\_171213) is another VGAM592 host target gene. LOC255158 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255158, corresponding to a HOST TARGET binding site such as BIND-



ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255158 BINDING SITE, designated SEQ ID:46001, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25175] Another function of VGAM592 is therefore inhibition of LOC255158 (Accession XM\_171213). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255158. LOC90538 (Accession XM\_032401) is another VGAM592 host target gene. LOC90538 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90538 BINDING SITE, designated SEQ ID:31657, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25176] Another function of VGAM592 is therefore inhibition of LOC90538 (Accession XM\_032401). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC90538. LOC93380 (Accession XM\_051020) is another VGAM592 host target gene. LOC93380 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93380, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93380 BINDING SITE, designated SEQ ID:35726, to the nucleotide sequence of VGAM592 RNA, herein designated VGAM RNA, also designated SEQ ID:3303.

[25177] Another function of VGAM592 is therefore inhibition of LOC93380 (Accession XM\_051020). Accordingly, utilities of VGAM592 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93380. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 593 (VGAM593) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25178] VGAM593 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM593 was detected is described hereinabove with reference to Figs. 1–8.

[25179] VGAM593 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM593 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25180] VGAM593 gene encodes a VGAM593 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM593 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM593 precursor RNA is designated SEQ ID:579, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:579 is located at position 75792 relative to the genome of Gallid Herpesvirus 2.

[25181] VGAM593 precursor RNA folds onto itself, forming VGAM593 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25182] An enzyme complex designated DICER COMPLEX, `dices` the VGAM593 folded precursor RNA into VGAM593 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM593 RNA is designated SEQ ID:3304, and is provided hereinbelow with reference to the sequence listing part.

[25183] VGAM593 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM593 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM593 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25184] VGAM593 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM593 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM593 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM593 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM593 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[25185] The complementary binding of VGAM593 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM593 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM593 host target RNA into VGAM593 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25186] It is appreciated that VGAM593 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM593 host target genes. The mRNA of each one of this plurality of VGAM593 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM593 RNA, herein designated VGAM RNA, and which when bound by VGAM593 RNA causes inhibition of translation of respective one or more VGAM593 host target proteins.

[25187] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM593 gene, herein designated VGAM GENE, on one or more VGAM593 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25188] It is yet further appreciated that a function of VGAM593 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM593 correlate with, and may be deduced from, the identity of the host target genes which VGAM593 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25189] Nucleotide sequences of the VGAM593 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM593 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM593 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM593 are further described hereinbelow with reference to Table 1.

[25190] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM593 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM593 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25191] As mentioned hereinabove with reference to Fig. 1, a function of VGAM593 gene, herein designated VGAM is inhibition of expression of VGAM593 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM593 correlate with, and may be deduced from, the identity of the target genes which VGAM593 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25192] Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 3 (CBFA2T3, Accession NM\_005187) is a VGAM593 host target gene. CBFA2T3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by CBFA2T3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CBFA2T3 BINDING SITE, designated SEQ ID:11694, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25193] A function of VGAM593 is therefore inhibition of Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 3 (CBFA2T3, Accession NM\_005187). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBFA2T3. Growth Arrest-specific 11 (GAS11, Accession NM\_001481) is another VGAM593 host target gene. GAS11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAS11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAS11 BINDING SITE, designated SEQ ID:7222, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25194] Another function of VGAM593 is therefore inhibition of Growth Arrest-specific 11 (GAS11, Accession NM\_001481). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAS11. Nidogen (enactin) (NID, Accession NM\_002508) is another VGAM593 host target gene. NID BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NID, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NID BINDING SITE, designated SEQ ID:8341, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25195] Another function of VGAM593 is therefore inhibition of Nidogen (enactin) (NID, Accession NM\_002508). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NID. Nipsnap Homolog 1 (C. elegans) (NIPSNAP1, Accession NM\_003634) is another VGAM593 host target gene. NIPSNAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NIPSNAP1, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NIPSNAP1 BINDING SITE, designated SEQ ID:9703, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25196] Another function of VGAM593 is therefore inhibition of Nipsnap Homolog 1 (*C. elegans*) (NIPSNAP1, Accession NM\_003634). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NIPSNAP1. Ubiquitin Protein Ligase E3A (human papilloma virus E6-associated protein, Angelman syndrome) (UBE3A, Accession NM\_130838) is another VGAM593 host target gene. UBE3A BINDING SITE1 through UBE3A BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by UBE3A, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE3A BINDING SITE1 through UBE3A BINDING SITE3, designated SEQ ID:28359, SEQ ID:28363 and SEQ ID:6078 respectively, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3304.

[25197] Another function of VGAM593 is therefore inhibition of Ubiquitin Protein Ligase E3A (human papilloma virus E6-associated protein, Angelman syndrome) (UBE3A, Accession NM\_130838). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE3A. KIAA0141 (Accession NM\_014773) is another VGAM593 host target gene. KIAA0141 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0141, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0141 BINDING SITE, designated SEQ ID:16584, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25198] Another function of VGAM593 is therefore inhibition of KIAA0141 (Accession NM\_014773). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0141. KIAA1550 (Accession XM\_039393) is another VGAM593 host target gene. KIAA1550 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1550, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1550 BINDING SITE, designated SEQ ID:33067, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25199] Another function of VGAM593 is therefore inhibition of KIAA1550 (Accession XM\_039393). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1550. KIAA1956 (Accession XM\_085836) is another VGAM593 host target gene. KIAA1956 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1956, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1956 BINDING SITE, designated SEQ ID:38363, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25200] Another function of VGAM593 is therefore inhibition of

KIAA1956 (Accession XM\_085836). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1956. MGC17330 (Accession NM\_052880) is another VGAM593 host target gene. MGC17330 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC17330, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC17330 BINDING SITE, designated SEQ ID:27458, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25201] Another function of VGAM593 is therefore inhibition of MGC17330 (Accession NM\_052880). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC17330. NYD-SP11 (Accession NM\_031951) is another VGAM593 host target gene. NYD-SP11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NYD-SP11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of NYD-SP11 BINDING SITE, designated SEQ ID:25688, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25202] Another function of VGAM593 is therefore inhibition of NYD-SP11 (Accession NM\_031951). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP11. Zinc Finger Protein 33a (KOX 31) (ZNF33A, Accession XM\_166119) is another VGAM593 host target gene. ZNF33A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF33A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF33A BINDING SITE, designated SEQ ID:43895, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25203] Another function of VGAM593 is therefore inhibition of Zinc Finger Protein 33a (KOX 31) (ZNF33A, Accession XM\_166119). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with ZNF33A. LOC124602 (Accession XM\_058829) is another VGAM593 host target gene. LOC124602 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC124602, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124602 BINDING SITE, designated SEQ ID:36758, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25204] Another function of VGAM593 is therefore inhibition of LOC124602 (Accession XM\_058829). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124602. LOC130412 (Accession XM\_065708) is another VGAM593 host target gene. LOC130412 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC130412, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130412 BINDING SITE, designated SEQ ID:37291, to



the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25205] Another function of VGAM593 is therefore inhibition of LOC130412 (Accession XM\_065708). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130412. LOC203397 (Accession XM\_114695) is another VGAM593 host target gene. LOC203397 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203397 BINDING SITE, designated SEQ ID:43038, to the nucleotide sequence of VGAM593 RNA, herein designated VGAM RNA, also designated SEQ ID:3304.

[25206] Another function of VGAM593 is therefore inhibition of LOC203397 (Accession XM\_114695). Accordingly, utilities of VGAM593 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203397. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 594 (VGAM594) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25207] VGAM594 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM594 was detected is described hereinabove with reference to Figs. 1–8.

[25208] VGAM594 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Northern Cereal Mosaic Virus. VGAM594 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25209] VGAM594 gene encodes a VGAM594 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM594 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM594 precursor RNA is designated SEQ ID:580, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:580 is located at position 8565 relative to the genome of Northern Cereal Mosaic Virus.

[25210] VGAM594 precursor RNA folds onto itself, forming VGAM594 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25211] An enzyme complex designated DICER COMPLEX, `dices` the VGAM594 folded precursor RNA into VGAM594 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM594 RNA is designated SEQ ID:3305, and is provided hereinbelow with reference to the sequence listing part.

[25212] VGAM594 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM594 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM594 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25213] VGAM594 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM594 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM594 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM594 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM594 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25214] The complementary binding of VGAM594 RNA, herein designated VGAM RNA, to host target binding sites on VGAM594 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM594 host target RNA into VGAM594 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25215] It is appreciated that VGAM594 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM594 host target genes. The mRNA of each one of this plurality of VGAM594 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM594 RNA, herein designated VGAM RNA, and which when bound by VGAM594 RNA causes inhibition of translation of respective one or more VGAM594 host target proteins.

[25216] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM594 gene, herein designated VGAM GENE, on one or more VGAM594 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25217] It is yet further appreciated that a function of VGAM594 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of viral infection by Northern Cereal Mosaic Virus. Specific functions, and accordingly utilities, of VGAM594 correlate with, and may be deduced from, the

identity of the host target genes which VGAM594 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25218] Nucleotide sequences of the VGAM594 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM594 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM594 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM594 are further described hereinbelow with reference to Table 1.

[25219] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM594 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM594 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25220] As mentioned hereinabove with reference to Fig. 1, a function of VGAM594 gene, herein designated VGAM is inhibition of expression of VGAM594 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM594 correlate with, and may be deduced from, the identity of the target genes which VGAM594

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25221] Amyotrophic Lateral Sclerosis 2 (juvenile) (ALS2, Accession NM\_020919) is a VGAM594 host target gene. ALS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALS2 BINDING SITE, designated SEQ ID:21931, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25222] A function of VGAM594 is therefore inhibition of Amyotrophic Lateral Sclerosis 2 (juvenile) (ALS2, Accession NM\_020919). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALS2. HTRA3 (Accession XM\_114416) is another VGAM594 host target gene. HTRA3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HTRA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide



sequences of HTRA3 BINDING SITE, designated SEQ ID:42942, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25223] Another function of VGAM594 is therefore inhibition of HTRA3 (Accession XM\_114416). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTRA3. Kynurenine 3-monooxygenase (kynurenine 3-hydroxylase) (KMO, Accession NM\_003679) is another VGAM594 host target gene. KMO BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KMO, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KMO BINDING SITE, designated SEQ ID:9780, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25224] Another function of VGAM594 is therefore inhibition of Kynurenine 3-monooxygenase (kynurenine 3-hydroxylase) (KMO, Accession NM\_003679), a gene which may play a role in encephalic photoreception. Ac-

cordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KMO. The function of KMO and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM162. Laminin, Alpha 4 (LAMA4, Accession NM\_002290) is another VGAM594 host target gene. LAMA4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LAMA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LAMA4 BINDING SITE, designated SEQ ID:8070, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25225] Another function of VGAM594 is therefore inhibition of Laminin, Alpha 4 (LAMA4, Accession NM\_002290), a gene which mediates the attachment, migration and organization of cells into tissues. Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LAMA4. The function of LAMA4 and its association with various

diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM300. Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Accession NM\_003842) is another VGAM594 host target gene. TNFRSF10B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFRSF10B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFRSF10B BINDING SITE, designated SEQ ID:9942, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25226] Another function of VGAM594 is therefore inhibition of Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Accession NM\_003842), a gene which forms complex that induces apoptosis. Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFRSF10B. The function of TNFRSF10B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM400. Wingless-type MMTV Integra-

tion Site Family, Member 10B (WNT10B, Accession NM\_003394) is another VGAM594 host target gene. WNT10B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WNT10B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WNT10B BINDING SITE, designated SEQ ID:9432, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25227] Another function of VGAM594 is therefore inhibition of Wingless-type MMTV Integration Site Family, Member 10B (WNT10B, Accession NM\_003394), a gene which is a ligand for members of the frizzled family of seven trans-membrane receptors and may be a signaling molecule. Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WNT10B. The function of WNT10B has been established by previous studies. Several members of the Wnt gene family have been shown to cause mammary tumors in mice. Using degenerate primer PCR on human genomic DNA and specific PCR of cDNA libraries, Bui et al.

(1997) isolated a Wnt gene that had not previously been described in human. It is the human homolog of mouse Wnt10b, which had been shown to be one of the oncogenes cooperating with FGF3 (OMIM Ref. No. 164950) in the development of mouse mammary tumor virus (MMTV)–induced mammary carcinomas in mice. The human WNT10B sequence is 88 and 95% identical to the murine gene at nucleotide and amino acid levels, respectively. By YAC and fluorescence in situ hybridization (FISH) mapping, Bui et al. (1997) localized the gene to 12q13, a chromosomal region frequently rearranged in human tumors and also containing the WNT1 gene (OMIM Ref. No. 164820). WNT10B expression was not observed in normal and benign proliferations of human breast tissue but was found to be elevated in 3 of 50 primary breast carcinomas. Southern blot analysis of the carcinoma expressing the highest level of WNT10B showed no amplification or rearrangement of the gene. Hardiman et al. (1997) demonstrated that the WNT10B gene encodes a 389–amino acid protein with 96.6% sequence identity to mouse Wnt10b. The expression pattern showed that it is synthesized in many adult tissues with the highest levels found in heart and skeletal muscle. Ross et al. (2000)

showed that WNT signaling, likely mediated by WNT10B, is a molecular switch that governs adipogenesis. WNT signaling maintains preadipocytes in an undifferentiated state through inhibition of the adipogenic transcription factors CEBPA (OMIM Ref. No. 116897) and PPAR-gamma (OMIM Ref. No. 601487). When WNT signaling in preadipocytes is prevented by overexpression of axin (OMIM Ref. No. 603816) or dominant-negative TCF4 (OMIM Ref. No. 602272), these cells differentiate into adipocytes. Disruption of WNT signaling also causes transdifferentiation of myoblasts into adipocytes in vitro, highlighting the importance of this pathway not only in adipocyte differentiation but also in mesodermal cell fate determination. By PCR typing of a human/rodent monochromosomal panel and FISH, Hardiman et al. (1997) mapped the WNT10B gene to chromosome 12q13.1. By analyzing human genome draft sequence, Kirikoshi et al. (2001) determined that WNT10B is encoded by 5 exons and is clustered with WNT1 (OMIM Ref. No. 164820) in a head-to-head manner with an interval of less than 7 kb. They hypothesized that the WNT1-WNT10B gene cluster and the WNT6 (OMIM Ref. No. 604663)-WNT10A (OMIM Ref. No. 606268) gene cluster on chromosome 2 might be

due to duplication of an ancestral WNT gene cluster.

[25228] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25229] Kirikoshi, H.; Sekihara, H.; Katoh, M. : WNT10A and WNT6, clustered in human chromosome 2q35 region with head-to-tail manner, are strongly coexpressed in SW480 cells. *Biochem. Biophys. Res. Commun.* 283: 798–805, 2001. ; and

[25230] Ross, S. E.; Hemati, N.; Longo, K. A.; Bennett, C. N.; Lucas, P. C.; Erickson, R. L.; MacDougald, O. A. : Inhibition of adipogenesis by Wnt signaling. *Science* 289: 950–953, 2000.

[25231] Further studies establishing the function and utilities of WNT10B are found in John Hopkins OMIM database record ID 601906, and in cited publications numbered 8886–888 and 12748 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CDC14 Cell Division Cycle 14 Homolog B (*S. cerevisiae*) (CDC14B, Accession NM\_033332) is another VGAM594 host target gene. CDC14B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDC14B, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDC14B BINDING SITE, designated SEQ ID:27176, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25232] Another function of VGAM594 is therefore inhibition of CDC14 Cell Division Cycle 14 Homolog B (*S. cerevisiae*) (CDC14B, Accession NM\_033332). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDC14B. CSRP2 Binding Protein (CSRP2BP, Accession XM\_046520) is another VGAM594 host target gene. CSRP2BP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSRP2BP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSRP2BP BINDING SITE, designated SEQ ID:34737, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25233] Another function of VGAM594 is therefore inhibition of CSRP2 Binding Protein (CSRP2BP, Accession XM\_046520).



Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSRP2BP. DKFZP434D146 (Accession NM\_015595) is another VGAM594 host target gene. DKFZP434D146 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434D146, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434D146 BINDING SITE, designated SEQ ID:17874, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25234] Another function of VGAM594 is therefore inhibition of DKFZP434D146 (Accession NM\_015595). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434D146. KIAA0435 (Accession NM\_014801) is another VGAM594 host target gene. KIAA0435 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0435, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of KIAA0435 BINDING SITE, designated SEQ ID:16726, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25235] Another function of VGAM594 is therefore inhibition of KIAA0435 (Accession NM\_014801). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0435. KIAA0444 (Accession XM\_030999) is another VGAM594 host target gene. KIAA0444 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0444, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0444 BINDING SITE, designated SEQ ID:31247, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25236] Another function of VGAM594 is therefore inhibition of KIAA0444 (Accession XM\_030999). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0444. KIAA0563 (Accession NM\_014834) is another

VGAM594 host target gene. KIAA0563 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0563, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0563 BINDING SITE, designated SEQ ID:16845, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25237] Another function of VGAM594 is therefore inhibition of KIAA0563 (Accession NM\_014834). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0563. Phytanoyl-CoA Hydroxylase Interacting Protein (PHYHIP, Accession NM\_014759) is another VGAM594 host target gene. PHYHIP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PHYHIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PHYHIP BINDING SITE, designated SEQ ID:16512, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3305.

[25238] Another function of VGAM594 is therefore inhibition of Phytanoyl-CoA Hydroxylase Interacting Protein (PHYHIP, Accession NM\_014759). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PHYHIP. PRO1843 (Accession NM\_018507) is another VGAM594 host target gene. PRO1843 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO1843, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1843 BINDING SITE, designated SEQ ID:20574, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25239] Another function of VGAM594 is therefore inhibition of PRO1843 (Accession NM\_018507). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1843. RIL (Accession NM\_003687) is another VGAM594 host target gene. RIL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

RIL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RIL BINDING SITE, designated SEQ ID:9798, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25240] Another function of VGAM594 is therefore inhibition of RIL (Accession NM\_003687). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RIL. TUSP (Accession NM\_020245) is another VGAM594 host target gene. TUSP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TUSP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TUSP BINDING SITE, designated SEQ ID:21536, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25241] Another function of VGAM594 is therefore inhibition of TUSP (Accession NM\_020245). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TUSP.

LOC144845 (Accession NM\_138474) is another VGAM594 host target gene. LOC144845 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144845, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144845 BINDING SITE, designated SEQ ID:28823, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25242] Another function of VGAM594 is therefore inhibition of LOC144845 (Accession NM\_138474). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144845. LOC150290 (Accession XM\_086863) is another VGAM594 host target gene. LOC150290 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150290, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150290 BINDING SITE, designated SEQ ID:38934, to the nucleotide sequence of VGAM594 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3305.

[25243] Another function of VGAM594 is therefore inhibition of LOC150290 (Accession XM\_086863). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150290. LOC254423 (Accession XM\_173286) is another VGAM594 host target gene. LOC254423 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254423 BINDING SITE, designated SEQ ID:46531, to the nucleotide sequence of VGAM594 RNA, herein designated VGAM RNA, also designated SEQ ID:3305.

[25244] Another function of VGAM594 is therefore inhibition of LOC254423 (Accession XM\_173286). Accordingly, utilities of VGAM594 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254423. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 595 (VGAM595) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25245] VGAM595 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM595 was detected is described hereinabove with reference to Figs. 1–8.

[25246] VGAM595 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Northern Cereal Mosaic Virus. VGAM595 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25247] VGAM595 gene encodes a VGAM595 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM595 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM595 precursor RNA is designated SEQ ID:581, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:581 is located at position 9694 relative to the genome of Northern Cereal Mosaic Virus.

[25248] VGAM595 precursor RNA folds onto itself, forming



VGAM595 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25249] An enzyme complex designated DICER COMPLEX, `dices` the VGAM595 folded precursor RNA into VGAM595 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM595 RNA is designated SEQ ID:3306, and is provided hereinbelow with reference to the sequence listing part.

[25250] VGAM595 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM595 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM595 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25251] VGAM595 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM595 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM595 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM595 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM595 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25252] The complementary binding of VGAM595 RNA, herein designated VGAM RNA, to host target binding sites on VGAM595 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM595 host target RNA into VGAM595 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25253] It is appreciated that VGAM595 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM595 host target genes. The mRNA of each one of this plurality of VGAM595 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM595 RNA, herein designated VGAM RNA, and which when bound by VGAM595 RNA causes inhibition of translation of respective one or more VGAM595 host target proteins.

[25254] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM595 gene, herein designated VGAM GENE, on one or more VGAM595 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25255] It is yet further appreciated that a function of VGAM595 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of viral infection by Northern Cereal Mosaic Virus. Specific functions, and accordingly utilities, of VGAM595 correlate with, and may be deduced from, the identity of the host target genes which VGAM595 binds

and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25256] Nucleotide sequences of the VGAM595 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM595 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM595 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM595 are further described hereinbelow with reference to Table 1.

[25257] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM595 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM595 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25258] As mentioned hereinabove with reference to Fig. 1, a function of VGAM595 gene, herein designated VGAM is inhibition of expression of VGAM595 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM595 correlate with, and may be deduced from, the identity of the target genes which VGAM595 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[25259] ATP-binding Cassette, Sub-family G (WHITE), Member 1 (ABCG1, Accession NM\_004915) is a VGAM595 host target gene. ABCG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABCG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCG1 BINDING SITE, designated SEQ ID:11352, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25260] A function of VGAM595 is therefore inhibition of ATP-binding Cassette, Sub-family G (WHITE), Member 1 (ABCG1, Accession NM\_004915), a gene which transporter involved in macrophage lipid homeostasis. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCG1. The function of ABCG1 has been established by previous studies. In *Drosophila*, the 'White' (W), 'Scarlet' (St), and 'Brown' (Bw) proteins are members of the ATP-binding cassette (ABC) transporter superfamily of trans-membrane permeases and are involved in transporting

precursors of eye pigments. See 601691. A functional ABC transporter unit contains 2 nucleotide-binding domains and 2 hydrophobic domains. The W, Bw, and St proteins contain only 1 of each domain, and so W is thought to form heterodimers with St or Bw to assemble functional transporters. Using RACE assays, Lorkowski et al. (2001) determined that the ABCG1 gene contains 5 exons more than what was previously reported, 4 upstream and 1 downstream of the previous exon 1, and spans 97 kb. The novel exons are predicted to encode at least 5 novel transcripts. Additional promoter regions were identified upstream of exons 1 and 5, respectively. The first promoter contains putative SP1 (OMIM Ref. No. 189906) and nuclear factor kappa-B (see OMIM Ref. No. 164011) binding sites, but no sterol response elements or retinoid X receptor (see OMIM Ref. No. 180245) binding sites. The second promoter contains all 4 of these binding-site types. Both promoters, however, were found to be responsive in macrophages to hydroxycholesterol and retinoic acid. Chen et al. (1996) reported a DNA polymorphism with 62% heterozygosity due to variation of a poly(T) region in the 3-prime untranslated region of hW. Croop et al. (1997) identified a polymorphic (CA)<sub>n</sub> repeat that is either intra-

genic or within 20 kb of the 3-prime end of hW. By analysis of somatic cell hybrids and by linkage analysis, Chen et al. (1996) mapped the hW gene to 21q22.3. This assignment was confirmed by Croop et al. (1997) using fluorescence in situ hybridization and by Savary et al. (1996) using in situ hybridization. By in situ hybridization, Savary et al. (1996) mapped the ABC8 gene to mouse chromosome 17, region A2-B, a region that shows homology of synteny with human chromosome 21q22.2-q22.3.

[25261] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25262] Chen, H.; Rossier, C.; Lalioti, M. D.; Lynn, A.; Chakravarti, A.; Perrin, G.; Antonarakis, S. E. : Cloning of the cDNA for a human homologue of the *Drosophila* white gene and mapping to chromosome 21q22.3. *Am. J. Hum. Genet.* 59: 66-75, 1996. ; and

[25263] Lorkowski, S.; Rust, S.; Engel, T.; Jung, E.; Tegelkamp, K.; Galinski, E. A.; Assmann, G.; Cullen, P. : Genomic sequence and structure of the human ABCG1 (ABC8) gene. *Biochem. Biophys. R.*

[25264] Further studies establishing the function and utilities of ABCG1 are found in John Hopkins OMIM database record



ID 603076, and in cited publications numbered 1062–1067 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Adenosine A1 Receptor (ADORA1, Accession NM\_000674) is another VGAM595 host target gene. ADORA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADORA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADORA1 BINDING SITE, designated SEQ ID:6330, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25265] Another function of VGAM595 is therefore inhibition of Adenosine A1 Receptor (ADORA1, Accession NM\_000674), a gene which the activity of this receptor is mediated by G proteins which inhibit adenylyl cyclase. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADORA1. The function of ADORA1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with

reference to VGAM234.CD28 Antigen (Tp44) (CD28, Accession NM\_006139) is another VGAM595 host target gene. CD28 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CD28, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD28 BINDING SITE, designated SEQ ID:12783, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25266] Another function of VGAM595 is therefore inhibition of CD28 Antigen (Tp44) (CD28, Accession NM\_006139), a gene which possibly involved in t-cell activation. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD28. The function of CD28 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM281.Citron (rho-interacting, serine/threonine kinase 21) (CIT, Accession XM\_045786) is another VGAM595 host target gene. CIT BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CIT, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CIT BINDING SITE, designated SEQ ID:34565, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25267] Another function of VGAM595 is therefore inhibition of Citron (rho-interacting, serine/threonine kinase 21) (CIT, Accession XM\_045786), a gene which is increased several-fold by coexpression of constitutively active Rho . Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CIT. The function of CIT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM393.Chloride Channel, Calcium Activated, Family Member 3 (CLCA3, Accession NM\_004921) is another VGAM595 host target gene. CLCA3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CLCA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of CLCA3 BINDING SITE, designated SEQ ID:11356, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25268] Another function of VGAM595 is therefore inhibition of Chloride Channel, Calcium Activated, Family Member 3 (CLCA3, Accession NM\_004921), a gene which is similar to calcium-activated chloride channel family. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCA3. The function of CLCA3 has been established by previous studies. Members of the CLCA family of calcium-activated chloride channels, such as human CLCA1 (OMIM Ref. No. 603906) and bovine lung-endothelial cell adhesion molecule-1 (Lu-ECAM-1), are translated as approximately 125-kD proteins that are cleaved to form transmembrane heterodimers consisting of approximately 90- and 35-kD polypeptides. See CLCA1 for additional information on the CLCA family. By screening a human spleen cDNA library with a Lu-ECAM-1 cDNA and by RACE, Gruber and Pauli (1999) isolated a 3.6-kb cDNA encoding CLCA3. The CLCA3 cDNA is similar in length and sequence to the cDNAs of previously cloned family mem-

bers. However, unlike all previously known CLCA cDNAs, the CLCA3 cDNA does not have a long open reading frame (ORF), but instead contains 2 smaller ORFs. The authors demonstrated that only 1 of these ORFs is of biologic significance and that it is expressed in mammalian cells as a secreted 37-kD glycoprotein. The deduced 262-amino acid CLCA3 protein corresponds to the N-terminal extracellular domain of other family members. RT-PCR detected CLCA3 expression in all human tissues examined. Gruber and Pauli (1999) verified the sequence of the spleen CLCA3 cDNA by isolating and sequencing a CLCA3 cDNA from human trachea. They concluded that CLCA3 is a structurally divergent member of the CLCA family and that it does not function as a channel protein.

[25269] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25270] Gruber, A. D.; Pauli, B. U. : Clustering of the human CLCA gene family on the short arm of chromosome 1 (1p22-31). *Genome* 42: 1030-1032, 1999. ; and

[25271] Gruber, A. D.; Pauli, B. U. : Molecular cloning and biochemical characterization of a truncated, secreted member of the human family of  $\text{Ca}^{2+}$ -activated  $\text{Cl}^-$  channels.

[25272] Further studies establishing the function and utilities of CLCA3 are found in John Hopkins OMIM database record ID 604337, and in cited publications numbered 7393 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cytochrome P450, Subfamily XIX (aromatization of androgens) (CYP19, Accession NM\_031226) is another VGAM595 host target gene. CYP19 BINDING SITE1 and CYP19 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CYP19, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP19 BINDING SITE1 and CYP19 BINDING SITE2, designated SEQ ID:25268 and SEQ ID:5558 respectively, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25273] Another function of VGAM595 is therefore inhibition of Cytochrome P450, Subfamily XIX (aromatization of androgens) (CYP19, Accession NM\_031226), a gene which catalyzes the last steps of estrogen biosynthesis. Accordingly, utilities of VGAM595 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with CYP19. The function of CYP19 and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM508. MDM1 (Accession NM\_020128) is another VGAM595 host target gene.

MDM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MDM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MDM1 BINDING SITE, designated SEQ ID:21321, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25274] Another function of VGAM595 is therefore inhibition of MDM1 (Accession NM\_020128). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MDM1. Nuclear RNA Export Factor 2 (NXF2, Accession NM\_017809) is another VGAM595 host target gene. NXF2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NXF2, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NXF2 BINDING SITE, designated SEQ ID:19459, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25275] Another function of VGAM595 is therefore inhibition of Nuclear RNA Export Factor 2 (NXF2, Accession NM\_017809), a gene which is involved in the export of mrna from the nucleus to the cytoplasm. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NXF2. The function of NXF2 has been established by previous studies. By searching EST databases for homologs of NXF1 and by RT-PCR analysis, Herold et al. (2000) obtained cDNAs encoding NXF2, NXF3 (OMIM Ref. No. 300316), NXF4 (OMIM Ref. No. 300318), and NXF5 (OMIM Ref. No. 300319). The deduced 626-amino acid NXF2 protein has the conserved domain structure of NXF1, including a noncanonical RNP-type RNA-binding domain (RBD), 4 leucine-rich repeats (LRRs), a nuclear transport factor-2 (NTF2; 605813)-like domain that allows heterodimerization with NTF2-related export pro-



tein-1 (NXT1; 605811), and a ubiquitin-associated domain that mediates interactions with nucleoporins. Binding analysis showed that NXF1, NXF2, and NXF3 interact with E1BAP5 (OMIM Ref. No. 605800), as well as with NXT1 and NXT2 (OMIM Ref. No. 300320). The RBDs of NXF1 and NXF2, but not that of NXF3, were found to bind RNA. Only NXF1, however, could promote RNA export mediated by the constitutive transport element of simian type D retrovirus. Both NXF1 and NXF2, but not NXF3, through their C-terminal NWD loop, could bind to the nucleoporins CAN (NUP214; 114350), NUP153 (OMIM Ref. No. 603948), and NUP62 (OMIM Ref. No. 605815). Only NXF1 could bind to NUP98 (OMIM Ref. No. 601021). Fluorescence microscopy demonstrated expression of NXF2 in the nucleoplasm and the nuclear envelope, but it was excluded from the nucleolus. CAT reporter and Western blot assays showed that coexpression of NXF1 or NXF2, but not NXF3, with NXT1 or NXT2 activated CAT expression, suggesting that under these conditions NXF2 can stimulate RNA export. The LRRs and NTF2-like domains are required for export activity. By cDNA subtraction of mouse somatic tissue cDNA from spermatogonia cDNA, database searching, and screening a testis cDNA library, Wang et al.

(2001) also identified NXF2.

[25276] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25277] Herold, A.; Suyama, M.; Rodrigues, J. P.; Braun, I. C.; Kutay, U.; Carmo-Fonseca, M.; Bork, P.; Izaurralde, E. : TAP (NXF1) belongs to a multigene family of putative RNA export factors with a conserved modular architecture. *Molec. Cell. Biol.* 20: 8996–9008, 2000. ; and

[25278] Wang, P. J.; McCarrey, J. R.; Yang, F.; Page, D. C. : An abundance of X-linked genes expressed in spermatogonia. *Nature Genet.* 27: 422–426, 2001.

[25279] Further studies establishing the function and utilities of NXF2 are found in John Hopkins OMIM database record ID 300315, and in cited publications numbered 9444 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. BH-protocadherin (brain-heart) (PCDH7, Accession NM\_032456) is another VGAM595 host target gene. PCDH7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDH7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of PCDH7 BINDING SITE, designated SEQ ID:26218, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25280] Another function of VGAM595 is therefore inhibition of BH-protocadherin (brain-heart) (PCDH7, Accession NM\_032456). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH7. RAD54B (Accession NM\_134434) is another VGAM595 host target gene. RAD54B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAD54B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAD54B BINDING SITE, designated SEQ ID:28678, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25281] Another function of VGAM595 is therefore inhibition of RAD54B (Accession NM\_134434), a gene which is involved in dna repair and mitotic recombination. Accordingly, utilities of VGAM595 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with RAD54B. The function of RAD54B has been established by previous studies. RAD54B, a member of the SNF2/SWI2 superfamily (see OMIM Ref. No. 600014), is part of a complex involved in the recombinational repair of DNA damage. Hiramoto et al. (1999) described the isolation of a member of the SNF2 superfamily characterized by sequence motifs similar to those in DNA and RNA helicases. The gene, designated RAD54B, shows significant homology to the RAD54 gene (OMIM Ref. No. 603615). The RAD54B cDNA was predicted to encode a protein of 910 amino acids. Northern blot analysis detected a 3.2-kb transcript highly expressed in testis and spleen, which are active in meiotic and mitotic recombination.

[25282] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25283] Hiramoto, T.; Nakanishi, T.; Sumiyoshi, T.; Fukuda, T.; Matsuura, S.; Tauchi, H.; Komatsu, K.; Shibasaki, Y.; Inui, H.; Watatani, M.; Yasutomi, M.; Sumii, K.; Kajiyama, G.; Kamada, N.; Miyagawa, K.; Kamiya, K. : Mutations of a novel human RAD54 homologue, RAD54B, in primary cancer. *Oncogene* 18: 3422–3426, 1999. ; and

[25284] Miyagawa, K.; Tsuruga, T.; Kinomura, A.; Usui, K.; Katsura, M.; Tashiro, S.; Mishima, H.; Tanaka, K. : A role for RAD54B in homologous recombination in human cells. EMBO J. 21: 175–180.

[25285] Further studies establishing the function and utilities of RAD54B are found in John Hopkins OMIM database record ID 604289, and in cited publications numbered 1102–1104 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Family 2 (facilitated glucose transporter), Member 3 (SLC2A3, Accession NM\_006931) is another VGAM595 host target gene. SLC2A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC2A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC2A3 BINDING SITE, designated SEQ ID:13814, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25286] Another function of VGAM595 is therefore inhibition of Solute Carrier Family 2 (facilitated glucose transporter), Member 3 (SLC2A3, Accession NM\_006931), a gene which

probably is a neuronal glucose transporter. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC2A3. The function of SLC2A3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. Transient Receptor Potential Cation Channel, Subfamily C, Member 5 (TRPC5, Accession NM\_012471) is another VGAM595 host target gene. TRPC5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPC5 BINDING SITE, designated SEQ ID:14850, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25287] Another function of VGAM595 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily C, Member 5 (TRPC5, Accession NM\_012471). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with TRPC5. Wolf–Hirschhorn Syndrome Candidate 1 (WHSC1, Accession NM\_007331) is another VGAM595 host target gene. WHSC1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by WHSC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WHSC1 BINDING SITE, designated SEQ ID:14250, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25288] Another function of VGAM595 is therefore inhibition of Wolf–Hirschhorn Syndrome Candidate 1 (WHSC1, Accession NM\_007331), a gene which binds covalently to and repairs g/t mismatches. Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WHSC1. The function of WHSC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200.AAK1 (Accession NM\_014911) is another VGAM595 host target gene. AAK1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by AAK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AAK1 BINDING SITE, designated SEQ ID:17145, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25289] Another function of VGAM595 is therefore inhibition of AAK1 (Accession NM\_014911). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AAK1. AF020591 (Accession NM\_014480) is another VGAM595 host target gene. AF020591 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by AF020591, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AF020591 BINDING SITE, designated SEQ ID:15825, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25290] Another function of VGAM595 is therefore inhibition of AF020591 (Accession NM\_014480). Accordingly, utilities



of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AF020591. Bifunctional Apoptosis Regulator (BFAR, Accession XM\_027311) is another VGAM595 host target gene. BFAR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BFAR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BFAR BINDING SITE, designated SEQ ID:30480, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25291] Another function of VGAM595 is therefore inhibition of Bifunctional Apoptosis Regulator (BFAR, Accession XM\_027311). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BFAR. Chromosome 15 Open Reading Frame 5 (C15orf5, Accession NM\_030944) is another VGAM595 host target gene. C15orf5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C15orf5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of C15orf5 BINDING SITE, designated SEQ ID:25215, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25292] Another function of VGAM595 is therefore inhibition of Chromosome 15 Open Reading Frame 5 (C15orf5, Accession NM\_030944). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C15orf5. CED-6 (Accession NM\_016315) is another VGAM595 host target gene. CED-6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CED-6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CED-6 BINDING SITE, designated SEQ ID:18434, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25293] Another function of VGAM595 is therefore inhibition of CED-6 (Accession NM\_016315). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CED-6.

DKFZP761C169 (Accession XM\_042059) is another VGAM595 host target gene. DKFZP761C169 BINDING SITE1 and DKFZP761C169 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DKFZP761C169, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP761C169 BINDING SITE1 and DKFZP761C169 BINDING SITE2, designated SEQ ID:33677 and SEQ ID:33678 respectively, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25294] Another function of VGAM595 is therefore inhibition of DKFZP761C169 (Accession XM\_042059). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP761C169. FLJ10956 (Accession NM\_018283) is another VGAM595 host target gene. FLJ10956 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10956, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

FLJ10956 BINDING SITE, designated SEQ ID:20278, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25295] Another function of VGAM595 is therefore inhibition of FLJ10956 (Accession NM\_018283). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10956. FLJ11125 (Accession XM\_005318) is another VGAM595 host target gene. FLJ11125 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11125, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11125 BINDING SITE, designated SEQ ID:29978, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25296] Another function of VGAM595 is therefore inhibition of FLJ11125 (Accession XM\_005318). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11125. FLJ20294 (Accession NM\_017749) is another VGAM595 host target gene. FLJ20294 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ20294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20294 BINDING SITE, designated SEQ ID:19352, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25297] Another function of VGAM595 is therefore inhibition of FLJ20294 (Accession NM\_017749). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20294. FLJ21034 (Accession NM\_024940) is another VGAM595 host target gene. FLJ21034 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21034, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21034 BINDING SITE, designated SEQ ID:24484, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25298] Another function of VGAM595 is therefore inhibition of

FLJ21034 (Accession NM\_024940). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21034. FLJ23584 (Accession NM\_024588) is another VGAM595 host target gene. FLJ23584 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ23584, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23584 BINDING SITE, designated SEQ ID:23823, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25299] Another function of VGAM595 is therefore inhibition of FLJ23584 (Accession NM\_024588). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23584. FLJ30213 (Accession NM\_145008) is another VGAM595 host target gene. FLJ30213 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ30213, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ30213 BINDING SITE, designated SEQ ID:29609, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25300] Another function of VGAM595 is therefore inhibition of FLJ30213 (Accession NM\_145008). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ30213. KIAA0089 (Accession XM\_046056) is another VGAM595 host target gene. KIAA0089 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0089, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0089 BINDING SITE, designated SEQ ID:34670, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25301] Another function of VGAM595 is therefore inhibition of KIAA0089 (Accession XM\_046056). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0089. KIAA1155 (Accession XM\_030864) is another

VGAM595 host target gene. KIAA1155 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1155 BINDING SITE, designated SEQ ID:31201, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25302] Another function of VGAM595 is therefore inhibition of KIAA1155 (Accession XM\_030864). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1155. KIAA1276 (Accession XM\_039169) is another VGAM595 host target gene. KIAA1276 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1276 BINDING SITE, designated SEQ ID:33020, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.



[25303] Another function of VGAM595 is therefore inhibition of KIAA1276 (Accession XM\_039169). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1276. KIAA1712 (Accession XM\_041497) is another VGAM595 host target gene. KIAA1712 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1712, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1712 BINDING SITE, designated SEQ ID:33540, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25304] Another function of VGAM595 is therefore inhibition of KIAA1712 (Accession XM\_041497). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1712. KIAA1775 (Accession NM\_033100) is another VGAM595 host target gene. KIAA1775 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1775, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1775 BINDING SITE, designated SEQ ID:26945, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25305] Another function of VGAM595 is therefore inhibition of KIAA1775 (Accession NM\_033100). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1775. MSP (Accession NM\_032046) is another VGAM595 host target gene. MSP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSP BINDING SITE, designated SEQ ID:25762, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25306] Another function of VGAM595 is therefore inhibition of MSP (Accession NM\_032046). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSP. My-

ozenin 2 (MYOZ2, Accession NM\_016599) is another VGAM595 host target gene. MYOZ2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYOZ2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYOZ2 BINDING SITE, designated SEQ ID:18694, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25307] Another function of VGAM595 is therefore inhibition of Myozenin 2 (MYOZ2, Accession NM\_016599). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYOZ2. P21 (CDKN1A)-activated Kinase 2 (PAK2, Accession XM\_039354) is another VGAM595 host target gene. PAK2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PAK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAK2 BINDING SITE, designated SEQ ID:33063, to the nucleotide sequence of VGAM595 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3306.

[25308] Another function of VGAM595 is therefore inhibition of P21 (CDKN1A)–activated Kinase 2 (PAK2, Accession XM\_039354). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAK2. PRO1430 (Accession NM\_018599) is another VGAM595 host target gene. PRO1430 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO1430, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1430 BINDING SITE, designated SEQ ID:20678, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25309] Another function of VGAM595 is therefore inhibition of PRO1430 (Accession NM\_018599). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1430. Sialyltransferase 4A (beta–galactoside alpha–2,3–sialyltransferase) (SIAT4A, Accession NM\_003033) is another VGAM595 host target gene. SIAT4A BINDING SITE

is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SIAT4A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIAT4A BINDING SITE, designated SEQ ID:8982, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25310] Another function of VGAM595 is therefore inhibition of Sialyltransferase 4A (beta-galactoside alpha-2,3-sialyltransferase) (SIAT4A, Accession NM\_003033). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIAT4A. TOPBP1 (Accession NM\_007027) is another VGAM595 host target gene. TOPBP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TOPBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOPBP1 BINDING SITE, designated SEQ ID:13888, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25311] Another function of VGAM595 is therefore inhibition of TOPBP1 (Accession NM\_007027). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOPBP1. LOC126603 (Accession XM\_060090) is another VGAM595 host target gene. LOC126603 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC126603, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126603 BINDING SITE, designated SEQ ID:37152, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25312] Another function of VGAM595 is therefore inhibition of LOC126603 (Accession XM\_060090). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126603. LOC129676 (Accession XM\_065341) is another VGAM595 host target gene. LOC129676 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC129676, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC129676 BINDING SITE, designated SEQ ID:37289, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25313] Another function of VGAM595 is therefore inhibition of LOC129676 (Accession XM\_065341). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129676. LOC143914 (Accession XM\_084654) is another VGAM595 host target gene. LOC143914 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC143914, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143914 BINDING SITE, designated SEQ ID:37637, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25314] Another function of VGAM595 is therefore inhibition of LOC143914 (Accession XM\_084654). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC143914. LOC144195 (Accession XM\_016498) is another VGAM595 host target gene. LOC144195 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144195, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144195 BINDING SITE, designated SEQ ID:30264, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25315] Another function of VGAM595 is therefore inhibition of LOC144195 (Accession XM\_016498). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144195. LOC149707 (Accession XM\_086641) is another VGAM595 host target gene. LOC149707 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149707, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149707 BINDING SITE, designated SEQ ID:38803, to the nucleotide sequence of VGAM595 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3306.

[25316] Another function of VGAM595 is therefore inhibition of LOC149707 (Accession XM\_086641). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149707. LOC150848 (Accession XM\_097959) is another VGAM595 host target gene. LOC150848 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150848 BINDING SITE, designated SEQ ID:41252, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25317] Another function of VGAM595 is therefore inhibition of LOC150848 (Accession XM\_097959). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150848. LOC150960 (Accession XM\_087059) is another VGAM595 host target gene. LOC150960 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150960, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150960 BINDING SITE, designated SEQ ID:39032, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25318] Another function of VGAM595 is therefore inhibition of LOC150960 (Accession XM\_087059). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150960. LOC154789 (Accession XM\_088043) is another VGAM595 host target gene. LOC154789 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154789, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154789 BINDING SITE, designated SEQ ID:39488, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25319] Another function of VGAM595 is therefore inhibition of LOC154789 (Accession XM\_088043). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC154789. LOC157226 (Accession XM\_033876) is another VGAM595 host target gene. LOC157226 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC157226, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157226 BINDING SITE, designated SEQ ID:31979, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25320] Another function of VGAM595 is therefore inhibition of LOC157226 (Accession XM\_033876). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157226. LOC158062 (Accession XM\_098861) is another VGAM595 host target gene. LOC158062 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC158062, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158062 BINDING SITE, designated SEQ ID:41916, to

the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25321] Another function of VGAM595 is therefore inhibition of LOC158062 (Accession XM\_098861). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158062. LOC200227 (Accession XM\_114162) is another VGAM595 host target gene. LOC200227 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200227, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200227 BINDING SITE, designated SEQ ID:42748, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25322] Another function of VGAM595 is therefore inhibition of LOC200227 (Accession XM\_114162). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200227. LOC200273 (Accession XM\_047698) is another VGAM595 host target gene. LOC200273 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC200273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200273 BINDING SITE, designated SEQ ID:35029, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25323] Another function of VGAM595 is therefore inhibition of LOC200273 (Accession XM\_047698). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200273. LOC256529 (Accession XM\_174314) is another VGAM595 host target gene. LOC256529 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256529, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256529 BINDING SITE, designated SEQ ID:46590, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25324] Another function of VGAM595 is therefore inhibition of LOC256529 (Accession XM\_174314). Accordingly, utilities

of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256529. LOC51068 (Accession NM\_015938) is another VGAM595 host target gene. LOC51068 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51068, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51068 BINDING SITE, designated SEQ ID:18057, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25325] Another function of VGAM595 is therefore inhibition of LOC51068 (Accession NM\_015938). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51068. LOC91496 (Accession XM\_038788) is another VGAM595 host target gene. LOC91496 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91496, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC91496 BINDING SITE, designated SEQ ID:32914, to the nucleotide sequence of VGAM595 RNA, herein designated VGAM RNA, also designated SEQ ID:3306.

[25326] Another function of VGAM595 is therefore inhibition of LOC91496 (Accession XM\_038788). Accordingly, utilities of VGAM595 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91496. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 596 (VGAM596) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25327] VGAM596 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM596 was detected is described hereinabove with reference to Figs. 1–8.

[25328] VGAM596 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Northern Cereal Mosaic Virus. VGAM596 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25329] VGAM596 gene encodes a VGAM596 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM596 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM596 precursor RNA is designated SEQ ID:582, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:582 is located at position 12057 relative to the genome of Northern Cereal Mosaic Virus.

[25330] VGAM596 precursor RNA folds onto itself, forming VGAM596 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25331] An enzyme complex designated DICER COMPLEX, `dices` the VGAM596 folded precursor RNA into VGAM596 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a



hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM596 RNA is designated SEQ ID:3307, and is provided hereinbelow with reference to the sequence listing part.

[25332] VGAM596 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM596 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM596 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25333] VGAM596 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM596 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM596 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM596 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM596 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25334] The complementary binding of VGAM596 RNA, herein designated VGAM RNA, to host target binding sites on VGAM596 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM596 host target RNA into VGAM596 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25335] It is appreciated that VGAM596 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM596 host target genes. The mRNA of each one of this plurality of VGAM596 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM596 RNA, herein designated VGAM RNA, and which when bound by VGAM596 RNA causes inhibition of translation of respective one or more VGAM596 host target proteins.

[25336] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM596 gene, herein designated VGAM GENE, on one or more VGAM596 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[25337] It is yet further appreciated that a function of VGAM596 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of viral infection by Northern Cereal Mosaic Virus. Specific functions, and accordingly utilities, of VGAM596 correlate with, and may be deduced from, the identity of the host target genes which VGAM596 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25338] Nucleotide sequences of the VGAM596 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM596 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM596 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM596 are further described hereinbelow with reference to Table 1.

[25339] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM596 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM596 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25340] As mentioned hereinabove with reference to Fig. 1, a function of VGAM596 gene, herein designated VGAM is inhibition of expression of VGAM596 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM596 correlate with, and may be deduced from, the identity of the target genes which VGAM596 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25341] Carboxypeptidase D (CPD, Accession NM\_001304) is a VGAM596 host target gene. CPD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CPD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CPD BINDING SITE, designated SEQ ID:6983, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25342] A function of VGAM596 is therefore inhibition of Car-

boxypeptidase D (CPD, Accession NM\_001304), a gene which is a membrane-bound metalloprotease. Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CPD. The function of CPD has been established by previous studies. The metallocarboxypeptidase family of enzymes is divided into 2 subfamilies based on sequence similarities. The pancreatic carboxypeptidase-like class includes carboxypeptidase A (OMIM Ref. No. 114850), carboxypeptidase B (OMIM Ref. No. 114852), CPA3 (OMIM Ref. No. 114851) and CPB2 (OMIM Ref. No. 603101). The regulatory B-type carboxypeptidase subfamily includes carboxypeptidase N (OMIM Ref. No. 603103), CPM (OMIM Ref. No. 114860), CPE, or H (OMIM Ref. No. 114855), and AEBP1 (OMIM Ref. No. 602981). In membrane fractions of mammalian cells, McGwire et al. (1997) identified a novel regulatory B-type carboxypeptidase that they designated carboxypeptidase D, or CPD. CPD is homologous to duck gp180, a hepatitis B virus-binding protein. By carrying out BLAST searches to identify human homologs of gp180, Tan et al. (1997) isolated cDNAs encoding CPD. The predicted 1,377-amino acid protein contains a signal sequence, 3 tandem carboxypepti-

dase homology domains, and a C-terminal putative trans-membrane domain. The 3 carboxypeptidase domains have sequence similarity to the regulatory B-type carboxypeptidase family. Overall, the amino acid sequences of CPD and gp180 are 75% identical. Northern blot analysis revealed CPD expression as multiple mRNAs in pancreas, placenta, heart, and skeletal muscle. By analysis of somatic cell hybrid panels, Riley et al. (1998) mapped the CPD gene to the centromeric region 17p11.1-q11.2.

[25343] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25344] McGwire, G. B.; Tan, F.; Michel, B.; Rehli, M.; Skidgel, R. A. : Identification of a membrane-bound carboxypeptidase as the mammalian homolog of duck gp180, a hepatitis B virus-binding protein. Life Sci. 60: 715-724, 1997. ; and

[25345] Riley, D. A.; Tan, F.; Miletich, D. J.; Skidgel, R. A. : Chromosomal localization of the genes for human carboxypeptidase D (CPD) and the active 50-kilodalton subunit of human carboxypep.

[25346] Further studies establishing the function and utilities of CPD are found in John Hopkins OMIM database record ID 603102, and in cited publications numbered 8489-8491

listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Dishevelled, Dsh Homolog 3 (Drosophila) (DVL3, Accession NM\_004423) is another VGAM596 host target gene. DVL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DVL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DVL3 BINDING SITE, designated SEQ ID:10689, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25347] Another function of VGAM596 is therefore inhibition of Dishevelled, Dsh Homolog 3 (Drosophila) (DVL3, Accession NM\_004423), a gene which regulates cell proliferation. Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DVL3. The function of DVL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM57. Reticulon 3 (RTN3, Accession XM\_058207) is another VGAM596 host target gene. RTN3 BINDING SITE is HOST TARGET binding site



found in the 3' untranslated region of mRNA encoded by RTN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RTN3 BINDING SITE, designated SEQ ID:36584, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25348] Another function of VGAM596 is therefore inhibition of Reticulon 3 (RTN3, Accession XM\_058207), a gene which is a member of the reticulon (neuroendocrine-specific, NSP) family. Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RTN3. The function of RTN3 has been established by previous studies. The reticulons are a group of highly conserved genes with preferential expression in neuroendocrine tissues. During a subtraction cloning between macula and peripheral retina, Moreira et al. (1999) isolated a novel member of the reticulon gene family, which they designated reticulon-3. The mRNA for RTN3 was approximately 3-fold more abundant in macula than in peripheral retina. The 2,527-bp cDNA encodes a predicted 236-amino acid protein that shows strong sequence similarity with other members of the RTN

gene family (see, OMIM Ref. No., e.g., 600865). Northern blot analysis showed that RTN3 is widely expressed in human tissues, with highest expression in the brain. The RTN3 gene contains 7 exons and spans more than 15 kb. By use of somatic cell hybrid and radiation hybrid panels, Moreira et al. (1999) mapped the RTN3 gene to 11q13, between markers D11S4535 and D11S4627. Southern blot analysis identified the presence of at least one pseudo-gene that was subsequently localized to chromosome 4

[25349] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25350] Moreira, E. F.; Jaworski, C. J.; Rodriguez, I. R. : Cloning of a novel member of the reticulon gene family (RTN3): gene structure and chromosomal localization to 11q13. *Genomics* 58: 73–81, 1999. ; and

[25351] Moreira, E. F.; Jaworski, C. J.; Rodriguez, I. R. : Cloning of a novel member of the reticulon gene family (RTN3): gene structure and chromosomal localization to 11q13. *Genomics* 58: 73–81.

[25352] Further studies establishing the function and utilities of RTN3 are found in John Hopkins OMIM database record ID 604249, and in cited publications numbered 692 listed in

the bibliography section hereinbelow, which are also hereby incorporated by reference. TEM6 (Accession NM\_022748) is another VGAM596 host target gene. TEM6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TEM6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TEM6 BINDING SITE, designated SEQ ID:22964, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25353] Another function of VGAM596 is therefore inhibition of TEM6 (Accession NM\_022748), a gene which displays elevated expression during tumor angiogenesis. Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TEM6. The function of TEM6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM175. Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736) is another VGAM596 host target gene. XPR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by XPR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XPR1 BINDING SITE, designated SEQ ID:11123, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25354] Another function of VGAM596 is therefore inhibition of Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736), a gene which is a putative G protein-coupled receptor and a target for xenotropic and polytropic murine leukemia retroviruses. Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XPR1. The function of XPR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM430.MGC29898 (Accession NM\_145048) is another VGAM596 host target gene. MGC29898 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC29898, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of MGC29898 BINDING SITE, designated SEQ ID:29679, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25355] Another function of VGAM596 is therefore inhibition of MGC29898 (Accession NM\_145048). Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC29898. LOC145955 (Accession XM\_096912) is another VGAM596 host target gene. LOC145955 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145955, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145955 BINDING SITE, designated SEQ ID:40642, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25356] Another function of VGAM596 is therefore inhibition of LOC145955 (Accession XM\_096912). Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC145955. LOC152905 (Accession XM\_017966) is another VGAM596 host target gene. LOC152905 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152905, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152905 BINDING SITE, designated SEQ ID:30330, to the nucleotide sequence of VGAM596 RNA, herein designated VGAM RNA, also designated SEQ ID:3307.

[25357] Another function of VGAM596 is therefore inhibition of LOC152905 (Accession XM\_017966). Accordingly, utilities of VGAM596 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152905. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 597 (VGAM597) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25358] VGAM597 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM597 was detected is described hereinabove with reference to Figs. 1–8.

[25359] VGAM597 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM597 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25360] VGAM597 gene encodes a VGAM597 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM597 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM597 precursor RNA is designated SEQ ID:583, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:583 is located at position 10633 relative to the genome of Transmissible Gastroenteritis Virus.

[25361] VGAM597 precursor RNA folds onto itself, forming VGAM597 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25362] An enzyme complex designated DICER COMPLEX, `dices` the VGAM597 folded precursor RNA into VGAM597 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 62%) nucleotide sequence of VGAM597 RNA is designated SEQ ID:3308, and is provided hereinbelow with reference to the sequence listing part.

[25363] VGAM597 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM597 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM597 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25364] VGAM597 RNA, herein designated VGAM RNA, binds com-



plementarily to one or more host target binding sites located in untranslated regions of VGAM597 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM597 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM597 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM597 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[25365] The complementary binding of VGAM597 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM597 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM597 host target RNA into VGAM597 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25366] It is appreciated that VGAM597 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM597 host target genes. The mRNA of each one of this plurality of VGAM597 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM597 RNA, herein designated VGAM RNA, and which when bound by VGAM597 RNA causes inhibition of translation of respective one or more VGAM597 host target proteins.

[25367] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM597 gene, herein designated VGAM GENE, on one or more VGAM597 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25368] It is yet further appreciated that a function of VGAM597 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM597 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM597 correlate with, and may be deduced from, the identity of the host target genes which VGAM597 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25369] Nucleotide sequences of the VGAM597 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM597 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM597 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM597 are further described hereinbelow with reference to Table 1.

[25370] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM597 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM597 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25371] As mentioned hereinabove with reference to Fig. 1, a function of VGAM597 gene, herein designated VGAM is inhibition of expression of VGAM597 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM597 correlate with, and may be deduced from, the identity of the target genes which VGAM597 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25372] CGG Triplet Repeat Binding Protein 1 (CGGBP1, Accession NM\_003663) is a VGAM597 host target gene. CGGBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CGGBP1,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CGGBP1 BINDING SITE, designated SEQ ID:9737, to the nucleotide sequence of VGAM597 RNA, herein designated VGAM RNA, also designated SEQ ID:3308.

[25373] A function of VGAM597 is therefore inhibition of CGG Triplet Repeat Binding Protein 1 (CGGBP1, Accession NM\_003663). Accordingly, utilities of VGAM597 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CGGBP1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 598 (VGAM598) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25374] VGAM598 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM598 was detected is described hereinabove with reference to Figs. 1–8.

[25375] VGAM598 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM598 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25376] VGAM598 gene encodes a VGAM598 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM598 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM598 precursor RNA is designated SEQ ID:584, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:584 is located at position 7593 relative to the genome of Transmissible Gastroenteritis Virus.

[25377] VGAM598 precursor RNA folds onto itself, forming VGAM598 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25378] An enzyme complex designated DICER COMPLEX, `dices` the VGAM598 folded precursor RNA into VGAM598 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 58%) nucleotide sequence of VGAM598 RNA is designated SEQ ID:3309, and is provided hereinbelow with reference to the sequence listing part.

[25379] VGAM598 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM598 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM598 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25380] VGAM598 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM598 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM598 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM598 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM598 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25381] The complementary binding of VGAM598 RNA, herein designated VGAM RNA, to host target binding sites on VGAM598 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM598 host tar-



get RNA into VGAM598 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25382] It is appreciated that VGAM598 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM598 host target genes. The mRNA of each one of this plurality of VGAM598 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM598 RNA, herein designated VGAM RNA, and which when bound by VGAM598 RNA causes inhibition of translation of respective one or more VGAM598 host target proteins.

[25383] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM598 gene, herein designated VGAM GENE, on one or more VGAM598 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25384] It is yet further appreciated that a function of VGAM598 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM598 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM598 correlate with, and may be deduced from, the identity of the host target genes which VGAM598 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25385] Nucleotide sequences of the VGAM598 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM598 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM598 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM598 are further

described hereinbelow with reference to Table 1.

[25386] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM598 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM598 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25387] As mentioned hereinabove with reference to Fig. 1, a function of VGAM598 gene, herein designated VGAM is inhibition of expression of VGAM598 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM598 correlate with, and may be deduced from, the identity of the target genes which VGAM598 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25388] BCRP2 (Accession XM\_031102) is a VGAM598 host target gene. BCRP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCRP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCRP2 BINDING SITE, designated SEQ

ID:31272, to the nucleotide sequence of VGAM598 RNA, herein designated VGAM RNA, also designated SEQ ID:3309.

[25389] A function of VGAM598 is therefore inhibition of BCRP2 (Accession XM\_031102). Accordingly, utilities of VGAM598 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCRP2. Estrogen-related Receptor Gamma (ESRRG, Accession XM\_039053) is another VGAM598 host target gene. ESRRG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESRRG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRG BINDING SITE, designated SEQ ID:32996, to the nucleotide sequence of VGAM598 RNA, herein designated VGAM RNA, also designated SEQ ID:3309.

[25390] Another function of VGAM598 is therefore inhibition of Estrogen-related Receptor Gamma (ESRRG, Accession XM\_039053), a gene which Estrogen-related receptor gamma. Accordingly, utilities of VGAM598 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESRRG. The function of ESRRG

and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM359.FLJ20147 (Accession NM\_017687) is another VGAM598 host target gene. FLJ20147 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20147, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20147 BINDING SITE, designated SEQ ID:19242, to the nucleotide sequence of VGAM598 RNA, herein designated VGAM RNA, also designated SEQ ID:3309.

[25391] Another function of VGAM598 is therefore inhibition of FLJ20147 (Accession NM\_017687). Accordingly, utilities of VGAM598 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20147. FLJ22060 (Accession NM\_024612) is another VGAM598 host target gene. FLJ22060 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22060, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ22060 BINDING SITE, designated SEQ ID:23866, to the nucleotide sequence of VGAM598 RNA, herein designated VGAM RNA, also designated SEQ ID:3309.

[25392] Another function of VGAM598 is therefore inhibition of FLJ22060 (Accession NM\_024612). Accordingly, utilities of VGAM598 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22060. HIC (Accession XM\_041273) is another VGAM598 host target gene. HIC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HIC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HIC BINDING SITE, designated SEQ ID:33496, to the nucleotide sequence of VGAM598 RNA, herein designated VGAM RNA, also designated SEQ ID:3309.

[25393] Another function of VGAM598 is therefore inhibition of HIC (Accession XM\_041273). Accordingly, utilities of VGAM598 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HIC. TAF2 RNA Polymerase II, TATA Box Binding Protein (TBP)-associated Factor, 150kDa (TAF2, Accession

NM\_003184) is another VGAM598 host target gene. TAF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TAF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAF2 BINDING SITE, designated SEQ ID:9158, to the nucleotide sequence of VGAM598 RNA, herein designated VGAM RNA, also designated SEQ ID:3309.

[25394] Another function of VGAM598 is therefore inhibition of TAF2 RNA Polymerase II, TATA Box Binding Protein (TBP)-associated Factor, 150kDa (TAF2, Accession NM\_003184). Accordingly, utilities of VGAM598 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAF2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 599 (VGAM599) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25395] VGAM599 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM599 was detected is described hereinabove with reference to Figs. 1–8.

[25396] VGAM599 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM599 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25397] VGAM599 gene encodes a VGAM599 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM599 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM599 precursor RNA is designated SEQ ID:585, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:585 is located at position 5831 relative to the genome of Transmissible Gastroenteritis Virus.

[25398] VGAM599 precursor RNA folds onto itself, forming VGAM599 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence



of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25399] An enzyme complex designated DICER COMPLEX, `dices` the VGAM599 folded precursor RNA into VGAM599 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM599 RNA is designated SEQ ID:3310, and is provided hereinbelow with reference to the sequence listing part.

[25400] VGAM599 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM599 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM599 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25401] VGAM599 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM599 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM599 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM599 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM599 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[25402] The complementary binding of VGAM599 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM599 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM599 host target RNA into VGAM599 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25403] It is appreciated that VGAM599 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM599 host target genes. The mRNA of each one of this plurality of VGAM599 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM599 RNA, herein designated VGAM RNA, and which when bound by VGAM599 RNA causes inhibition of translation of respective one or more VGAM599 host target proteins.

[25404] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM599 gene, herein designated VGAM GENE, on one or more VGAM599 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25405] It is yet further appreciated that a function of VGAM599 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM599 correlate with, and may be deduced from, the identity of the host target genes which VGAM599 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25406] Nucleotide sequences of the VGAM599 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM599 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM599 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM599 are further described hereinbelow with reference to Table 1.

[25407] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM599 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM599 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25408] As mentioned hereinabove with reference to Fig. 1, a function of VGAM599 gene, herein designated VGAM is inhibition of expression of VGAM599 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM599 correlate with, and may be deduced from, the identity of the target genes which VGAM599 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25409] Adducin 3 (gamma) (ADD3, Accession NM\_016824) is a VGAM599 host target gene. ADD3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADD3, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADD3 BINDING SITE, designated SEQ ID:18819, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25410] A function of VGAM599 is therefore inhibition of Adducin 3 (gamma) (ADD3, Accession NM\_016824), a gene which membrane-cytoskeleton-associated protein that promotes the assembly of the spectrin-actin network. Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADD3. The function of ADD3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM579. Chloride Channel 6 (CLCN6, Accession NM\_021735) is another VGAM599 host target gene. CLCN6 BINDING SITE1 through CLCN6 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CLCN6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

CLCN6 BINDING SITE1 through CLCN6 BINDING SITE3, designated SEQ ID:22339, SEQ ID:22344 and SEQ ID:6962 respectively, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25411] Another function of VGAM599 is therefore inhibition of Chloride Channel 6 (CLCN6, Accession NM\_021735), a gene which is a voltage-gated chloride channel. Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCN6. The function of CLCN6 has been established by previous studies. Members of the mammalian CLCN family of voltage-gated chloride channels display differential tissue distribution and perform diverse functions. Nomura et al. (1994) identified a partial human CLCN6 cDNA, which they called KIAA0046. Northern blot analysis revealed that CLCN6 was expressed widely. Using the partial cDNA sequence of Nomura et al. (1994), Brandt and Jentsch (1995) cloned human cerebral cortex cDNAs that covered the entire CLCN6 coding region. The predicted 869-amino acid protein was called CLC6 by them. The amino acid sequence of CLCN6 is 45% identical to that of CLCN7 (OMIM Ref. No. 602727) but only 23 to 29%

identical to the sequences of other known CLCNs. Therefore, Brandt and Jentsch (1995) stated that CLCN6 and CLCN7 together define a new branch of the chloride channel protein family. By Northern blot analysis, Brandt and Jentsch (1995) found that CLCN6 was expressed as an approximately 6-kb mRNA in all tissues examined. Eggermont et al. (1997) identified 4 different CLCN6 cDNAs that represent alternatively spliced transcripts. Nomura et al. (1994) mapped the CLCN6 gene to chromosome 1 using a somatic cell hybrid panel. By fluorescence in situ hybridization, Brandt and Jentsch (1995) refined the localization of the CLCN6 gene to 1p36. They noted that 2 genes encoding kidney-specific chloride channels, CLCNKA (OMIM Ref. No. 602024) and CLCNKB (OMIM Ref. No. 602023), also map to 1p36.

[25412] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25413] REFERENCES 1. Brandt, S.; Jentsch, T. J. : CLC-6 and CLC-7 are two novel broadly expressed members of the CLC chloride channel family. FEBS Lett. 377: 15-20, 1995. ; and

[25414] Eggermont, J.; Buyse, G.; Voets, T.; Tytgat, J.; De Smedt,



H.; Droogmans, G. : Alternative splicing of CLC-6 (a member of the CLC chloride-channel family) transcripts generates three tr.

[25415] Further studies establishing the function and utilities of CLCN6 are found in John Hopkins OMIM database record ID 602726, and in cited publications numbered 8588-858 and 2255 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. MAD2 Mitotic Arrest Deficient-like 1 (yeast) (MAD2L1, Accession NM\_002358) is another VGAM599 host target gene. MAD2L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAD2L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAD2L1 BINDING SITE, designated SEQ ID:8171, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25416] Another function of VGAM599 is therefore inhibition of MAD2 Mitotic Arrest Deficient-like 1 (yeast) (MAD2L1, Accession NM\_002358), a gene which may monitor the completeness of the spindle-kinetochore attachment. delays

the onset of anaphase when this process is not complete. Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAD2L1. The function of MAD2L1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM176. Origin Recognition Complex, Subunit 4-like (yeast) (ORC4L, Accession XM\_030582) is another VGAM599 host target gene. ORC4L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ORC4L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ORC4L BINDING SITE, designated SEQ ID:31091, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25417] Another function of VGAM599 is therefore inhibition of Origin Recognition Complex, Subunit 4-like (yeast) (ORC4L, Accession XM\_030582), a gene which may be required for initiation of DNA replication and has a putative nucleotide triphosphate binding motif. Accordingly, utili-

ties of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ORC4L. The function of ORC4L has been established by previous studies. In *S. cerevisiae*, sites at which DNA replication initiates are recognized by a 6-subunit origin recognition complex (ORC). The yeast ORC components have been designated ORC1 to 6. By searching an expressed sequence tag database, Quintana et al. (1997) identified mouse and human cDNAs with homology to yeast ORC4. The predicted 436-amino acid human ORC4L protein, which they called HsORC4P, shares 29% sequence identity with yeast ORC4. Antibodies against ORC4L detected a 45-kD doublet on immunoblots of human cell lysates. Immunoprecipitation studies revealed that ORC4L associates with multiple cellular proteins, including ORC2L (OMIM Ref. No. 601182), *in vivo*. By analysis of somatic cell hybrids and by fluorescence *in situ* hybridization, Eki et al. (1998) mapped the ORC4L gene to 2q22-q23.

[25418] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25419] Eki, T.; Dean, F. B.; Kohda, A.; Okumura, K.; Abe, M.; Murakami, Y.; Ishiai, M.; Satomoto, K.; Hurwitz, J.; O'Donnell,

M.; Hanaoka, F. : Assignment1 of the homologue of the yeast origin recognition complex subunit ORC4 (ORC4L) to human chromosome band 2q22–q23 by in situ hybridization and somatic cell hybrid analysis. Cytogenet. Cell Genet. 81: 89–90, 1998. ; and

[25420] Quintana, D. G.; Hou, Z.; Thome, K. C.; Hendricks, M.; Saha, P.; Dutta, A. : Identification of HsORC4, a member of the human origin of replication recognition complex. J. Biol. Chem. 27.

[25421] Further studies establishing the function and utilities of ORC4L are found in John Hopkins OMIM database record ID 603056, and in cited publications numbered 8481 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RNA Binding Motif Protein 3 (RBM3, Accession XM\_047024) is another VGAM599 host target gene. RBM3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RBM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RBM3 BINDING SITE, designated SEQ ID:34894, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3310.

[25422] Another function of VGAM599 is therefore inhibition of RNA Binding Motif Protein 3 (RBM3, Accession XM\_047024). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RBM3. Transforming Growth Factor, Beta Receptor I (activin A receptor type II-like kinase, 53kDa) (TGFB1, Accession NM\_004612) is another VGAM599 host target gene. TGFB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TGFB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TGFB1 BINDING SITE, designated SEQ ID:10951, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25423] Another function of VGAM599 is therefore inhibition of Transforming Growth Factor, Beta Receptor I (activin A receptor type II-like kinase, 53kDa) (TGFB1, Accession NM\_004612), a gene which forms a complex with TGF beta type II receptor and acts as signal transducer. Accordingly, utilities of VGAM599 include diagnosis, preven-

tion and treatment of diseases and clinical conditions associated with TGFBR1. The function of TGFBR1 has been established by previous studies. Ebner et al. (1993) cloned a murine serine/threonine kinase receptor that shares a conserved extracellular domain with the type II TGF-beta receptor. Overexpression of this receptor alone did not increase cell surface binding of TGF-beta, but coexpression with the type II TGF-beta receptor caused TGF-beta to bind to this receptor, which had the size of the type I TGF-beta receptor. Overexpression of this newly cloned receptor inhibited binding of TGF-beta to the type II receptor in a dominant-negative fashion. Combinatorial interactions and stoichiometric ratios between the type I and II receptors may therefore determine the extent of TGF-beta binding and the resulting biologic activities. Wang et al. (1994) reported that the type I receptor may be a natural ligand for immunophilin FKBP12 (OMIM Ref. No. 186945). The membrane-bound protein encoded by TGFBR1 binds TGF-beta and forms a heterodimeric complex with the TGF-beta II receptor. Ligand binding by TGF-beta I receptors is dependent on coexpression with type II receptors. Type II receptors alone can bind ligand, but require association with type I receptors for activation

of their kinase (signaling) function. Johnson et al. (1995) used PCR with a hybrid cell DNA panel and FISH to localize the TGFBR1 gene to 9q33–q34. By FISH, Pasche et al. (1998) localized the gene to 9q22. Kuan and Kono (1998) mapped the Tgfr1 gene to mouse chromosome 4. TGFB stimulation leads to phosphorylation and activation of SMAD2 (OMIM Ref. No. 601366) and SMAD3 (OMIM Ref. No. 603109), which form complexes with SMAD4 (OMIM Ref. No. 600993) that accumulate in the nucleus and regulate transcription of target genes. Inman et al. (2002) demonstrated that following TGFB stimulation of epithelial cells, receptors remain active for at least 3 to 4 hours, and continuous receptor activity is required to maintain active SMADs in the nucleus and for TGFB–induced transcription. Continuous nucleocytoplasmic shuttling of the SMADs during active TGFB signaling provides the mechanism whereby the intracellular transducers of the signal continuously monitor receptor activity. These data explain how, at all times, the concentration of active SMADs in the nucleus is directly dictated by the levels of activated receptors in the cytoplasm.

[25424] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [25425] Ebner, R.; Chen, R.-H.; Shum, L.; Lawler, S.; Zioncheck, T. F.; Lee, A.; Lopez, A. R.; Derynck, R. : Cloning of a type I TGF-beta receptor and its effect on TGF-beta binding to the type II receptor. Science 260: 1344-1348, 1993. ; and
- [25426] Inman, G. J.; Nicolas, F. J.; Hill, C. S. : Nucleocytoplasmic shuttling of Smads 2, 3, and 4 permits sensing of TGF-beta receptor activity. Molec. Cell 10: 283-294, 2002.
- [25427] Further studies establishing the function and utilities of TGFBR1 are found in John Hopkins OMIM database record ID 190181, and in cited publications numbered 2504-2509, 114 and 10040 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Potassium Large Conductance Calcium-activated Channel, Subfamily M, Beta Member 2 (KCNMB2, Accession NM\_005832) is another VGAM599 host target gene. KCNMB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNMB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNMB2 BINDING SITE, designated SEQ ID:12447, to the nucleotide sequence of VGAM599 RNA,



herein designated VGAM RNA, also designated SEQ ID:3310.

[25428] Another function of VGAM599 is therefore inhibition of Potassium Large Conductance Calcium-activated Channel, Subfamily M, Beta Member 2 (KCNMB2, Accession NM\_005832). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNMB2. KIAA1627 (Accession XM\_087571) is another VGAM599 host target gene. KIAA1627 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1627, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1627 BINDING SITE, designated SEQ ID:39345, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25429] Another function of VGAM599 is therefore inhibition of KIAA1627 (Accession XM\_087571). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1627. LOC152573 (Accession XM\_087488) is another

VGAM599 host target gene. LOC152573 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152573, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152573 BINDING SITE, designated SEQ ID:39289, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25430] Another function of VGAM599 is therefore inhibition of LOC152573 (Accession XM\_087488). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152573. LOC202451 (Accession XM\_117401) is another VGAM599 host target gene. LOC202451 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202451, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202451 BINDING SITE, designated SEQ ID:43440, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25431] Another function of VGAM599 is therefore inhibition of LOC202451 (Accession XM\_117401). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202451. LOC253039 (Accession XM\_171203) is another VGAM599 host target gene. LOC253039 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253039, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253039 BINDING SITE, designated SEQ ID:45994, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25432] Another function of VGAM599 is therefore inhibition of LOC253039 (Accession XM\_171203). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253039. LOC253782 (Accession XM\_171023) is another VGAM599 host target gene. LOC253782 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253782, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253782 BINDING SITE, designated SEQ ID:45800, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25433] Another function of VGAM599 is therefore inhibition of LOC253782 (Accession XM\_171023). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253782. LOC91801 (Accession NM\_138775) is another VGAM599 host target gene. LOC91801 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91801, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91801 BINDING SITE, designated SEQ ID:29010, to the nucleotide sequence of VGAM599 RNA, herein designated VGAM RNA, also designated SEQ ID:3310.

[25434] Another function of VGAM599 is therefore inhibition of LOC91801 (Accession NM\_138775). Accordingly, utilities of VGAM599 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC91801. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 600 (VGAM600) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25435] VGAM600 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM600 was detected is described hereinabove with reference to Figs. 1–8.

[25436] VGAM600 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM600 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25437] VGAM600 gene encodes a VGAM600 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM600 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM600 precursor RNA is designated SEQ ID:586, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:586 is located at position 5005 relative to the genome of Transmissible Gastroenteritis Virus.

[25438] VGAM600 precursor RNA folds onto itself, forming VGAM600 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25439] An enzyme complex designated DICER COMPLEX, `dices` the VGAM600 folded precursor RNA into VGAM600 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM600 RNA is designated SEQ ID:3311, and is provided hereinbelow with reference to the sequence listing part.

[25440] VGAM600 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM600 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM600 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25441] VGAM600 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM600 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM600 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM600 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM600 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[25442] The complementary binding of VGAM600 RNA, herein designated VGAM RNA, to host target binding sites on VGAM600 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM600 host target RNA into VGAM600 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25443] It is appreciated that VGAM600 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM600 host target genes. The mRNA of each one of this plurality of VGAM600 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM600 RNA, herein designated VGAM RNA, and which when bound by VGAM600 RNA causes in-



hibition of translation of respective one or more VGAM600 host target proteins.

[25444] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM600 gene, herein designated VGAM GENE, on one or more VGAM600 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25445] It is yet further appreciated that a function of VGAM600 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM600 include diagnosis, prevention and

treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM600 correlate with, and may be deduced from, the identity of the host target genes which VGAM600 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25446] Nucleotide sequences of the VGAM600 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM600 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM600 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM600 are further described hereinbelow with reference to Table 1.

[25447] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM600 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM600 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25448] As mentioned hereinabove with reference to Fig. 1, a function of VGAM600 gene, herein designated VGAM is inhibition of expression of VGAM600 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM600 correlate with, and may be deduced from, the identity of the target genes which VGAM600 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25449] Activation-induced Cytidine Deaminase (AICDA, Accession NM\_020661) is a VGAM600 host target gene. AICDA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AICDA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AICDA BINDING SITE, designated SEQ ID:21832, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25450] A function of VGAM600 is therefore inhibition of Activation-induced Cytidine Deaminase (AICDA, Accession NM\_020661), a gene which is a member of the cytidine deaminase family. Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AICDA. The function of AICDA has been established by previous studies. Muramatsu et al. (1999) isolated the gene encoding activation-

induced cytidine deaminase (Aid), a member of the cytidine deaminase family, from a murine B-cell lymphoma line induced by combined stimulation of transforming growth factor-beta (TGFB; 190180), interleukin-4 (IL4; 147780), and CD40 ligand (CD40L; 300386). Muto et al. (2000) isolated the human AID gene, which encodes a 198-amino acid protein containing a conserved cytidine deaminase motif. The human AID protein shares 92% amino acid identity with mouse Aid. RT-PCR analysis of 15 human tissues detected strong expression of AID mRNA in lymph nodes and tonsils. Petersen-Mahrt et al. (2002) hypothesized that the 3 gene diversification processes mediated by AICDA, somatic hypermutation, gene conversion, and class-switch recombination, may be initiated by DNA lesions at dC/dG pairs by AICDA, which has sequence homology to the RNA editing enzyme APOBEC1 (OMIM Ref. No. 600130). Expression of AICDA in E. coli confers a mutator phenotype yielding nucleotide transitions at dC/dG in a context-dependent manner. The mutation triggered by AICDA is enhanced by a deficiency of uracil-DNA glycosylase (UNG; 191525), indicating that AICDA functions by deaminating dC residues in DNA. Petersen-Mahrt et al. (2002) proposed that diversification of

functional Ig genes is triggered by AICDA-mediated deamination of dC residues in the Ig locus with the outcome, i.e., hypermutation phases 1 and 2, gene conversion, or switch recombination, dependent on the way in which the initiating dU/dG lesion is resolved. Muto et al. (2000) mapped the AID gene to 12p13 by FISH. Animal model experiments lend further support to the function of AICDA. Muramatsu et al. (2000) found that in the mouse, Aid deficiency caused a complete defect in class switching and showed a hyper-IgM phenotype with enlarged germinal centers containing strongly activated B cells before or after immunization. Mouse Aid  $-/-$  spleen cells stimulated in vitro with lipopolysaccharide (LPS) and cytokines failed to undergo CSR, although they expressed germline transcripts.

[25451] It is appreciated that the abovementioned animal model for AICDA is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[25452] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25453] Muramatsu, M.; Sankaranand, V. S.; Anant, S.; Sugai, M.;

Kinoshita, K.; Davidson, N. O.; Honjo, T. : Specific expression of activation-induced cytidine deaminase (AID), a novel member of the RNA-editing deaminase family in germinal center B cells. J. Biol. Chem. 274: 18470–18476, 1999. ; and

[25454] Muramatsu, M.; Kinoshita, K.; Fagarasan, S.; Yamada, S.; Shinkai, Y.; Honjo, T. : Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a pot.

[25455] Further studies establishing the function and utilities of AICDA are found in John Hopkins OMIM database record ID 605257, and in cited publications numbered 4410–4413, 479 and 9131–2317 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Coagulation Factor II (thrombin) Receptor (F2R, Accession NM\_001992) is another VGAM600 host target gene. F2R BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by F2R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F2R BINDING SITE, designated SEQ ID:7724, to the nucleotide sequence of VGAM600 RNA,

herein designated VGAM RNA, also designated SEQ ID:3311.

[25456] Another function of VGAM600 is therefore inhibition of Coagulation Factor II (thrombin) Receptor (F2R, Accession NM\_001992), a gene which Thrombin receptor; G protein-coupled receptor involved in platelet activation. Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F2R. The function of F2R and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM140. Rho-associated, Coiled-coil Containing Protein Kinase 2 (ROCK2, Accession XM\_038377) is another VGAM600 host target gene. ROCK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ROCK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ROCK2 BINDING SITE, designated SEQ ID:32837, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25457] Another function of VGAM600 is therefore inhibition of

Rho-associated, Coiled-coil Containing Protein Kinase 2 (ROCK2, Accession XM\_038377), a gene which regulates cytokinesis, smooth muscle contraction, the formation of actin stress fibers and focal adhesions. Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ROCK2. The function of ROCK2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM273. AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Accession NM\_080551) is another VGAM600 host target gene. AP1GBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AP1GBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP1GBP1 BINDING SITE, designated SEQ ID:27878, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25458] Another function of VGAM600 is therefore inhibition of AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Accession NM\_080551). Accordingly, utilities of VGAM600 in-



clude diagnosis, prevention and treatment of diseases and clinical conditions associated with AP1GBP1. ARSDR1 (Accession NM\_016026) is another VGAM600 host target gene. ARSDR1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ARSDR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARSDR1 BINDING SITE, designated SEQ ID:18109, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25459] Another function of VGAM600 is therefore inhibition of ARSDR1 (Accession NM\_016026). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARSDR1. FLJ12688 (Accession XM\_055071) is another VGAM600 host target gene. FLJ12688 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12688, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12688 BINDING SITE,

designated SEQ ID:36221, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25460] Another function of VGAM600 is therefore inhibition of FLJ12688 (Accession XM\_055071). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12688. FLJ23042 (Accession NM\_025157) is another VGAM600 host target gene. FLJ23042 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23042, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23042 BINDING SITE, designated SEQ ID:24795, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25461] Another function of VGAM600 is therefore inhibition of FLJ23042 (Accession NM\_025157). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23042. KIAA0391 (Accession NM\_014672) is another VGAM600 host target gene. KIAA0391 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by KIAA0391, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0391 BINDING SITE, designated SEQ ID:16141, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25462] Another function of VGAM600 is therefore inhibition of KIAA0391 (Accession NM\_014672). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0391. KIAA1364 (Accession XM\_032997) is another VGAM600 host target gene. KIAA1364 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1364, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1364 BINDING SITE, designated SEQ ID:31812, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25463] Another function of VGAM600 is therefore inhibition of

KIAA1364 (Accession XM\_032997). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1364. KIAA1586 (Accession XM\_166451) is another VGAM600 host target gene. KIAA1586 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1586, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1586 BINDING SITE, designated SEQ ID:44348, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25464] Another function of VGAM600 is therefore inhibition of KIAA1586 (Accession XM\_166451). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1586. MGC13017 (Accession NM\_080656) is another VGAM600 host target gene. MGC13017 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC13017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of MGC13017 BINDING SITE, designated SEQ ID:27945, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25465] Another function of VGAM600 is therefore inhibition of MGC13017 (Accession NM\_080656). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC13017. Protein Tyrosine Phosphatase, Non-receptor Type Substrate 1 (PTPNS1, Accession NM\_080792) is another VGAM600 host target gene. PTPNS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTPNS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPNS1 BINDING SITE, designated SEQ ID:28057, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25466] Another function of VGAM600 is therefore inhibition of Protein Tyrosine Phosphatase, Non-receptor Type Substrate 1 (PTPNS1, Accession NM\_080792). Accordingly, utilities of VGAM600 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with PTPNS1. RoXaN (Accession NM\_025013) is another VGAM600 host target gene. RoXaN BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RoXaN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RoXaN BINDING SITE, designated SEQ ID:24601, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25467] Another function of VGAM600 is therefore inhibition of RoXaN (Accession NM\_025013). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RoXaN. LOC148809 (Accession XM\_086325) is another VGAM600 host target gene. LOC148809 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC148809, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148809 BINDING SITE, designated SEQ ID:38593, to the nucleotide se-

quence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25468] Another function of VGAM600 is therefore inhibition of LOC148809 (Accession XM\_086325). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148809. LOC149606 (Accession XM\_086600) is another VGAM600 host target gene. LOC149606 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149606, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149606 BINDING SITE, designated SEQ ID:38784, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25469] Another function of VGAM600 is therefore inhibition of LOC149606 (Accession XM\_086600). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149606. LOC153579 (Accession XM\_087714) is another VGAM600 host target gene. LOC153579 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC153579, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153579 BINDING SITE, designated SEQ ID:39403, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25470] Another function of VGAM600 is therefore inhibition of LOC153579 (Accession XM\_087714). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153579. LOC200251 (Accession XM\_114173) is another VGAM600 host target gene. LOC200251 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200251 BINDING SITE, designated SEQ ID:42755, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25471] Another function of VGAM600 is therefore inhibition of LOC200251 (Accession XM\_114173). Accordingly, utilities



of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200251. LOC202052 (Accession XM\_117355) is another VGAM600 host target gene. LOC202052 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC202052, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202052 BINDING SITE, designated SEQ ID:43406, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25472] Another function of VGAM600 is therefore inhibition of LOC202052 (Accession XM\_117355). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202052. LOC90092 (Accession XM\_028862) is another VGAM600 host target gene. LOC90092 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC90092, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC90092 BINDING SITE, designated SEQ ID:30784, to the nucleotide sequence of VGAM600 RNA, herein designated VGAM RNA, also designated SEQ ID:3311.

[25473] Another function of VGAM600 is therefore inhibition of LOC90092 (Accession XM\_028862). Accordingly, utilities of VGAM600 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90092. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 601 (VGAM601) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25474] VGAM601 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM601 was detected is described hereinabove with reference to Figs. 1–8.

[25475] VGAM601 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM601 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25476] VGAM601 gene encodes a VGAM601 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM601 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM601 precursor RNA is designated SEQ ID:587, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:587 is located at position 10134 relative to the genome of Transmissible Gastroenteritis Virus.

[25477] VGAM601 precursor RNA folds onto itself, forming VGAM601 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25478] An enzyme complex designated DICER COMPLEX, `dices` the VGAM601 folded precursor RNA into VGAM601 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 66%) nucleotide sequence of VGAM601 RNA is designated SEQ ID:3312, and is provided hereinbelow with reference to the sequence listing part.

[25479] VGAM601 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM601 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM601 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25480] VGAM601 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM601 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM601 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM601 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM601 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25481] The complementary binding of VGAM601 RNA, herein designated VGAM RNA, to host target binding sites on VGAM601 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM601 host target RNA into VGAM601 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25482] It is appreciated that VGAM601 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM601 host target genes. The mRNA of each one of this plurality of VGAM601 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM601 RNA, herein designated VGAM RNA, and which when bound by VGAM601 RNA causes inhibition of translation of respective one or more VGAM601 host target proteins.

[25483] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM601 gene, herein designated VGAM GENE, on one or more VGAM601 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[25484] It is yet further appreciated that a function of VGAM601 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM601 correlate with, and may be deduced from, the identity of the host target genes which VGAM601 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25485] Nucleotide sequences of the VGAM601 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM601 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM601 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM601 are further described hereinbelow with reference to Table 1.

[25486] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM601 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM601 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25487] As mentioned hereinabove with reference to Fig. 1, a function of VGAM601 gene, herein designated VGAM is inhibition of expression of VGAM601 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM601 correlate with, and may be deduced from, the identity of the target genes which VGAM601 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25488] Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_004013) is a VGAM601 host target gene. DMD BINDING SITE1 through DMD BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DMD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DMD BINDING SITE1 through DMD BINDING SITE3, designated SEQ ID:10190, SEQ ID:10217 and SEQ ID:10229 respectively, to the nucleotide sequence of VGAM601 RNA, herein des-



ignated VGAM RNA, also designated SEQ ID:3312.

[25489] A function of VGAM601 is therefore inhibition of Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_004013), a gene which muscular dystrophy . Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DMD. The function of DMD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM218. Interleukin 18 Receptor Accessory Protein (IL18RAP, Accession NM\_003853) is another VGAM601 host target gene. IL18RAP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by IL18RAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL18RAP BINDING SITE, designated SEQ ID:9948, to the nucleotide sequence of VGAM601 RNA, herein designated VGAM RNA, also designated SEQ ID:3312.

[25490] Another function of VGAM601 is therefore inhibition of Interleukin 18 Receptor Accessory Protein (IL18RAP, Ac-

cession NM\_003853). Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL18RAP. Asparaginyl-tRNA Synthetase (NARS, Accession NM\_004539) is another VGAM601 host target gene. NARS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NARS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NARS BINDING SITE, designated SEQ ID:10889, to the nucleotide sequence of VGAM601 RNA, herein designated VGAM RNA, also designated SEQ ID:3312.

[25491] Another function of VGAM601 is therefore inhibition of Asparaginyl-tRNA Synthetase (NARS, Accession NM\_004539), a gene which is ASPARAGINYL-tRNA SYNTHETASE. Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NARS. The function of NARS has been established by previous studies. Using a DNA probe in human-rodent hybrid cells, Shows (1983) found that asparaginyl-tRNA synthetase segregated with peptidase A, a chromosome 18 marker. Cirullo et al. (1983) used the abbreviation-symbol 'asnS.' They isolated hybrids between human peripheral leukocytes and a temperature-sensitive CHO cell line with a thermolabile asparaginyl-tRNA synthetase. Hybrids selected at 39 degrees C required the presence of human chromosome 18. Temperature-resistant hybrid cells contained 2 forms of ASNRS: 1 highly thermal resistant, like the human enzyme, and 1 highly thermolabile, like the CHO mutant enzyme.

[25492] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25493] Cirullo, R. E.; Arredondo-Vega, F. X.; Smith, M.; Wasmuth, J. J. : Isolation and characterization of interspecific heat-

resistant hybrids between a temperature-sensitive Chinese hamster cell asparaginyl-tRNA synthetase mutant and normal human leukocytes: assignment of human asnS gene to chromosome 18. Somat. Cell Genet. 9: 215-233, 1983. ; and

[25494] Shows, T. B. : Personal Communication. Buffalo, N. Y., 1/11/1983.

[25495] Further studies establishing the function and utilities of NARS are found in John Hopkins OMIM database record ID 108410, and in cited publications numbered 1360-1361 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. TIRAP (Accession NM\_052887) is another VGAM601 host target gene. TIRAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIRAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIRAP BINDING SITE, designated SEQ ID:27471, to the nucleotide sequence of VGAM601 RNA, herein designated VGAM RNA, also designated SEQ ID:3312.

[25496] Another function of VGAM601 is therefore inhibition of TIRAP (Accession NM\_052887), a gene which is a adapter

involved in the TLR4 signaling pathway in the innate immune response. Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIRAP. The function of TIRAP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM189.FLJ23403 (Accession NM\_022068) is another VGAM601 host target gene. FLJ23403 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23403, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23403 BINDING SITE, designated SEQ ID:22611, to the nucleotide sequence of VGAM601 RNA, herein designated VGAM RNA, also designated SEQ ID:3312.

[25497] Another function of VGAM601 is therefore inhibition of FLJ23403 (Accession NM\_022068). Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23403. KIAA1948 (Accession XM\_091984) is another VGAM601 host target gene. KIAA1948 BINDING SITE is HOST TARGET

binding site found in the 3` untranslated region of mRNA encoded by KIAA1948, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1948 BINDING SITE, designated SEQ ID:40074, to the nucleotide sequence of VGAM601 RNA, herein designated VGAM RNA, also designated SEQ ID:3312.

[25498] Another function of VGAM601 is therefore inhibition of KIAA1948 (Accession XM\_091984). Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1948. LOC142893 (Accession XM\_096354) is another VGAM601 host target gene. LOC142893 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC142893, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC142893 BINDING SITE, designated SEQ ID:40320, to the nucleotide sequence of VGAM601 RNA, herein designated VGAM RNA, also designated SEQ ID:3312.

[25499] Another function of VGAM601 is therefore inhibition of

LOC142893 (Accession XM\_096354). Accordingly, utilities of VGAM601 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC142893. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 602 (VGAM602) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25500] VGAM602 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM602 was detected is described hereinabove with reference to Figs. 1–8.

[25501] VGAM602 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM602 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25502] VGAM602 gene encodes a VGAM602 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM602 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM602 precursor RNA is designated SEQ ID:588, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:588 is located at position 10388 relative to the genome of Transmissible Gastroenteritis Virus.

[25503] VGAM602 precursor RNA folds onto itself, forming VGAM602 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25504] An enzyme complex designated DICER COMPLEX, `dices` the VGAM602 folded precursor RNA into VGAM602 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 69%) nucleotide se-



quence of VGAM602 RNA is designated SEQ ID:3313, and is provided hereinbelow with reference to the sequence listing part.

[25505] VGAM602 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM602 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM602 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[25506] VGAM602 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM602 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM602 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM602 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM602 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[25507] The complementary binding of VGAM602 RNA, herein designated VGAM RNA, to host target binding sites on VGAM602 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM602 host target RNA into VGAM602 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25508] It is appreciated that VGAM602 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM602 host target genes. The mRNA of each one of this plurality of VGAM602 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM602 RNA, herein designated VGAM RNA, and which when bound by VGAM602 RNA causes inhibition of translation of respective one or more VGAM602 host target proteins.

[25509] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM602 gene, herein designated VGAM GENE, on one or more VGAM602 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25510] It is yet further appreciated that a function of VGAM602 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM602 correlate with, and may be deduced from, the identity of the host target genes which VGAM602 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25511] Nucleotide sequences of the VGAM602 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM602 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM602 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM602 are further described hereinbelow with reference to Table 1.

[25512] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM602 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM602 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25513] As mentioned hereinabove with reference to Fig. 1, a function of VGAM602 gene, herein designated VGAM is inhibition of expression of VGAM602 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM602 correlate with, and may be deduced from, the identity of the target genes which VGAM602 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25514] Adrenergic, Alpha-2A-, Receptor (ADRA2A, Accession NM\_000681) is a VGAM602 host target gene. ADRA2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADRA2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADRA2A BINDING SITE, designated SEQ ID:6338, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25515] A function of VGAM602 is therefore inhibition of Adrenergic, Alpha-2A-, Receptor (ADRA2A, Accession NM\_000681), a gene which mediates the effects of epinephrine and norepinephrine. Accordingly, utilities of

VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADRA2A. The function of ADRA2A has been established by previous studies. Hormones and drugs exert their physiologic and pharmacologic effects by interacting with specific plasma membrane receptors of responsive cells. Adrenergic receptors fall into 2 major classes, alpha and beta, each of which is subdivided into 2 subclasses, termed alpha-1 and alpha-2 and beta-1 and beta-2. The beta-adrenergic receptors, which stimulate, and the alpha-2-adrenergic receptors, which often inhibit adenylate cyclase, are coupled to guanine nucleotide regulatory proteins. Using an alpha-2-adrenergic receptor clone, Yang-Feng et al. (1987) mapped the ADRAR locus to 10q23-q25 by somatic cell hybridization and in situ hybridization. Kobilka et al. (1987) cloned the gene for the human platelet alpha-2-adrenergic receptor using oligonucleotides corresponding to the partial amino acid sequence of the purified receptor. The deduced amino acid sequence is most similar to those of human beta-2- and beta-1-adrenergic receptors. Similarities to the muscarinic cholinergic receptors are also evident. Two related genes were identified by low stringency Southern blot analysis. Hoehe et al. (1988)

identified a DraI RFLP of the ADRAR gene. By study of interspecific backcrosses, Oakey et al. (1991) assigned the Adra2r gene to the distal region of mouse chromosome 19. A substantial percentage of human pregnancies are lost as spontaneous abortions after implantation. This is often caused by an inadequately developed placenta. Proper development of the placental vascular system is essential to nutrient and gas exchange between mother and developing embryo. Philipp et al. (2002) showed that alpha-2-adrenoceptors, which are activated by adrenaline and noradrenaline, are important regulators of placental structure and function. Mice with deletions in the genes Adra2a, Adra2b, and Adra2c died between embryonic days 9.5 and 11.5 from a severe defect in yolk-sac and placenta development. In wildtype placentae, alpha-2-adrenoceptors are abundantly expressed in giant cells, which secrete angiogenic factors to initiate development of the placental vascular labyrinth. In placentae deficient in the 3 adrenoceptors encoded by the 3 genes deleted in these mice, the density of fetal blood vessels in the labyrinth was markedly lower than normal, leading to death of the embryos as a result of reduced oxygen and nutrient supply. Basal phosphorylation of the extracellular

signal-regulated kinases ERK1 (OMIM Ref. No. 601795) and ERK2 (OMIM Ref. No. 176948) was also lower than normal, suggesting that activation of the mitogen-activated protein kinase (MAP kinase) pathway by alpha-2-adrenoceptors is required for placenta and yolk-sac vascular development. Thus, alpha-2-adrenoceptors are essential at the placental interface between mother and embryo to establish the circulatory system of the placenta and thus maintain pregnancy.

[25516] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25517] Kobilka, B. K.; Matsui, H.; Kobilka, T. S.; Yang-Feng, T. L.; Francke, U.; Caron, M. G.; Lefkowitz, R. J.; Regan, J. W. : Cloning, sequencing, and expression of the gene coding for the human platelet alpha-2-adrenergic receptor. *Science* 238: 650-656, 1987. ; and

[25518] Philipp, M.; Brede, M. E.; Hadamek, K.; Gessler, M.; Lohse, M. J.; Hein, L. : Placental alpha-2-adrenoceptors control vascular development at the interface between mother and embryo. *Nat.*

[25519] Further studies establishing the function and utilities of ADRA2A are found in John Hopkins OMIM database record



ID 104210, and in cited publications numbered 12104–12113 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. BCRP2 (Accession XM\_031102) is another VGAM602 host target gene. BCRP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCRP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCRP2 BINDING SITE, designated SEQ ID:31271, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25520] Another function of VGAM602 is therefore inhibition of BCRP2 (Accession XM\_031102). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCRP2. Dynein, Axonemal, Heavy Polypeptide 9 (DNAH9, Accession NM\_004662) is another VGAM602 host target gene. DNAH9 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DNAH9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of DNAH9 BINDING SITE, designated SEQ ID:11032, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25521] Another function of VGAM602 is therefore inhibition of Dynein, Axonemal, Heavy Polypeptide 9 (DNAH9, Accession NM\_004662), a gene which is a microtubule-associated motor protein . Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNAH9. The function of DNAH9 has been established by previous studies. Dyneins are microtubule-associated motor protein complexes composed of several heavy, light, and intermediate chains. Two major classes of dyneins, axonemal and cytoplasmic, have been identified. The axonemal dyneins, found in cilia and flagella, are components of the outer and inner dynein arms attached to the peripheral microtubule doublets. See 603297. Vaughan et al. (1996) isolated human partial cDNAs encoding DNAH9 (HL20) and several other dynein heavy chains (DHCs). See DNAH5 (OMIM Ref. No. 603335). Sequence analysis revealed that DNAH9 is an axonemal DHC and is homologous to rat

DLP9. Milisav et al. (1996) identified a human testis cDNA encoding DNAH9, which they called DNEL1. Although the predicted 798-amino acid DNAH9 protein was the size of an intermediate or light dynein chain, it showed extensive homology to the C-terminal region of outer-arm axone-mal dynein beta-heavy chains from sea urchin and other species. The authors suggested that the similarity of DNAH9 to the beta-heavy chains indicates that these genes share a common origin. Northern blot analysis revealed that DNAH9 is expressed as a 3.2-kb mRNA exclusively in testis. Bartoloni et al. (2001) cloned an almost full-length cDNA encoding DNAH9. The deduced 4,486-amino acid protein contains several ATP/GTP-binding sites (P-loops), a microtubule-binding motif, a leucine zipper domain, and several phosphorylation sites. Analysis of 3 overlapping BACs determined that the DNAH9 gene contains 69 exons extending over 373 kb. RT-PCR analysis of nasal epithelium and testis RNA revealed several alternatively spliced transcripts.

[25522] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25523] Milisav, I.; Jones, M. H.; Affara, N. A. : Characterization of

a novel human dynein-related gene that is specifically expressed in testis. *Mammalian Genome* 7: 667-672, 1996.  
; and

[25524] Bartoloni, L.; Blouin, J.-L.; Maiti, A. K.; Sainsbury, A.; Rossier, C.; Gehrig, C.; She, J.-X.; Marron, M. P.; Lander, E. S.; Meeks, M.; Chung, E.; Armengot, M.; Jorissen, M.; Scott, H.

[25525] Further studies establishing the function and utilities of DNAH9 are found in John Hopkins OMIM database record ID 603330, and in cited publications numbered 7495, 7496-749 and 5344 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Glycine Receptor, Alpha 3 (GLRA3, Accession XM\_011092) is another VGAM602 host target gene. GLRA3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLRA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLRA3 BINDING SITE, designated SEQ ID:30168, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25526] Another function of VGAM602 is therefore inhibition of Glycine Receptor, Alpha 3 (GLRA3, Accession XM\_011092), a gene which increases the chloride conductance and thus produces hyperpolarization (inhibition of neuronal firing). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLRA3. The function of GLRA3 has been established by previous studies. The neuronal glycine receptor is a ligand-gated chloride channel composed of ligand-binding alpha and structural beta polypeptides. Kingsmore et al. (1994) mapped the gene encoding the alpha-3 subunit of the glycine receptor to mouse chromosome 8. The human and rat homologs of GLRA3 were cloned by Kuhse et al. (1990). The mouse gene was mapped in relation to Plat (plasminogen activator, tissue type; 173370), which is on human chromosome 8; thus, the human GLRA3 gene may be on human chromosome 8 also. This proved, however, not to be the case; Nikolic et al. (1998) mapped the GLRA3 gene to human 4q33-q34 by fluorescence in situ hybridization. By homology screening of a human fetal brain cDNA library, Nikolic et al. (1998) identified 2 alternative splice variants of the glycine receptor alpha-3 subunit. The amino acid se-

quence predicted for the long alpha-3 variant, designated alpha-3-L, was largely identical to the corresponding rat subunit. In contrast, the novel splice variant, designated alpha-3-K, lacked the coding sequence for 15 amino acids located within the cytoplasmic loop connecting transmembrane spanning region-3 (TM3) and TM4. Using P1 artificial chromosome (PAC) clones, they elucidated the structure of the GLRA3 gene. Two transcripts of 2.4 and 9 kb, corresponding to alpha-3-L and alpha-3-K, respectively, were identified and found to be widely distributed throughout the human central nervous system. Structural analysis of the GLRA3 gene revealed that the alpha-3-K transcript resulted from a complex splice event where excision of the novel exon 8A comprising the alternative sequence of 45 basepairs coincides with the persistence of a large intronic sequence in the 3-prime untranslated region. Functional expression in HEK 293 cells of alpha-3-L and alpha-3-K subunits resulted in the formation of glycine-gated chloride channels that differed significantly in desensitization behavior, thus defining the cytoplasmic loop as an important determinant of the channel inactivation kinetics

[25527] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [25528] Kuhse, J.; Schmieden, V.; Betz, H. : Identification and functional expression of a novel ligand binding subunit of the inhibitory glycine receptor. J. Biol. Chem. 265: 22317–22320, 1990. ; and
- [25529] Nikolic, Z.; Laube, B.; Weber, R. G.; Lichter, P.; Kioschis, P.; Poustka, A.; Mulhardt, C.; Becker, C.–M. : The human glycine receptor subunit alpha-3: GLRA3 gene structure, chromosomal.
- [25530] Further studies establishing the function and utilities of GLRA3 are found in John Hopkins OMIM database record ID 600421, and in cited publications numbered 10174–10176 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Insulin-like Growth Factor Binding Protein 3 (IGFBP3, Accession NM\_000598) is another VGAM602 host target gene. IGFBP3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IGFBP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IGFBP3 BINDING SITE, designated SEQ

ID:6196, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25531] Another function of VGAM602 is therefore inhibition of Insulin-like Growth Factor Binding Protein 3 (IGFBP3, Accession NM\_000598). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IGFBP3. Mannosyl (alpha-1,6-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession NM\_002408) is another VGAM602 host target gene. MGAT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGAT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAT2 BINDING SITE, designated SEQ ID:8233, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25532] Another function of VGAM602 is therefore inhibition of Mannosyl (alpha-1,6-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession



NM\_002408). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGAT2. Thrombomodulin (THBD, Accession NM\_000361) is another VGAM602 host target gene. THBD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by THBD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of THBD BINDING SITE, designated SEQ ID:5917, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25533] Another function of VGAM602 is therefore inhibition of Thrombomodulin (THBD, Accession NM\_000361). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with THBD. Zinc Finger Protein 278 (ZNF278, Accession NM\_014323) is another VGAM602 host target gene. ZNF278 BINDING SITE1 through ZNF278 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ZNF278, corresponding to HOST TARGET binding sites such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF278 BINDING SITE1 through ZNF278 BINDING SITE3, designated SEQ ID:15624, SEQ ID:25773 and SEQ ID:25782 respectively, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25534] Another function of VGAM602 is therefore inhibition of Zinc Finger Protein 278 (ZNF278, Accession NM\_014323), a gene which represses basal transcription as well as RNF4-mediated activation. Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF278. The function of ZNF278 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM414.DKFZp547H025 (Accession NM\_020161) is another VGAM602 host target gene. DKFZp547H025 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547H025, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of DKFZp547H025 BINDING SITE, designated SEQ ID:21373, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25535] Another function of VGAM602 is therefore inhibition of DKFZp547H025 (Accession NM\_020161). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547H025. FLJ10044 (Accession NM\_017980) is another VGAM602 host target gene. FLJ10044 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10044, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10044 BINDING SITE, designated SEQ ID:19710, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25536] Another function of VGAM602 is therefore inhibition of FLJ10044 (Accession NM\_017980). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10044. FLJ11164 (Accession NM\_018346) is another VGAM602

host target gene. FLJ11164 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11164, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11164 BINDING SITE, designated SEQ ID:20354, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25537] Another function of VGAM602 is therefore inhibition of FLJ11164 (Accession NM\_018346). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11164. Golgi Phosphoprotein 2 (GOLPH2, Accession NM\_016548) is another VGAM602 host target gene. GOLPH2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GOLPH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GOLPH2 BINDING SITE, designated SEQ ID:18624, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25538] Another function of VGAM602 is therefore inhibition of Golgi Phosphoprotein 2 (GOLPH2, Accession NM\_016548). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GOLPH2. KIAA0420 (Accession XM\_032693) is another VGAM602 host target gene. KIAA0420 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0420 BINDING SITE, designated SEQ ID:31721, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25539] Another function of VGAM602 is therefore inhibition of KIAA0420 (Accession XM\_032693). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0420. KIAA1024 (Accession XM\_044580) is another VGAM602 host target gene. KIAA1024 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1024, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1024 BINDING SITE, designated SEQ ID:34236, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25540] Another function of VGAM602 is therefore inhibition of KIAA1024 (Accession XM\_044580). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1024. KIAA1239 (Accession XM\_049078) is another VGAM602 host target gene. KIAA1239 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1239, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1239 BINDING SITE, designated SEQ ID:35338, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25541] Another function of VGAM602 is therefore inhibition of KIAA1239 (Accession XM\_049078). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1239. MGC4655 (Accession NM\_033309) is another VGAM602 host target gene. MGC4655 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4655, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4655 BINDING SITE, designated SEQ ID:27143, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25542] Another function of VGAM602 is therefore inhibition of MGC4655 (Accession NM\_033309). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4655. Polymerase (DNA directed), Epsilon 3 (p17 subunit) (POLE3, Accession NM\_017443) is another VGAM602 host target gene. POLE3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POLE3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POLE3 BINDING SITE,

designated SEQ ID:18899, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25543] Another function of VGAM602 is therefore inhibition of Polymerase (DNA directed), Epsilon 3 (p17 subunit) (POLE3, Accession NM\_017443). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POLE3. ZID (Accession NM\_006626) is another VGAM602 host target gene. ZID BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZID, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZID BINDING SITE, designated SEQ ID:13415, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25544] Another function of VGAM602 is therefore inhibition of ZID (Accession NM\_006626). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZID. LOC123283 (Accession XM\_071829) is another VGAM602 host target gene. LOC123283 BINDING SITE is HOST TAR-



GET binding site found in the 3' untranslated region of mRNA encoded by LOC123283, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC123283 BINDING SITE, designated SEQ ID:37424, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25545] Another function of VGAM602 is therefore inhibition of LOC123283 (Accession XM\_071829). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC123283. LOC144266 (Accession XM\_084795) is another VGAM602 host target gene. LOC144266 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144266, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144266 BINDING SITE, designated SEQ ID:37708, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25546] Another function of VGAM602 is therefore inhibition of

LOC144266 (Accession XM\_084795). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144266. LOC253782 (Accession XM\_171023) is another VGAM602 host target gene. LOC253782 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253782, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253782 BINDING SITE, designated SEQ ID:45795, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25547] Another function of VGAM602 is therefore inhibition of LOC253782 (Accession XM\_171023). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253782. LOC257354 (Accession XM\_170810) is another VGAM602 host target gene. LOC257354 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257354, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC257354 BINDING SITE, designated SEQ ID:45574, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25548] Another function of VGAM602 is therefore inhibition of LOC257354 (Accession XM\_170810). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257354. LOC51320 (Accession NM\_016626) is another VGAM602 host target gene. LOC51320 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51320, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51320 BINDING SITE, designated SEQ ID:18740, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25549] Another function of VGAM602 is therefore inhibition of LOC51320 (Accession NM\_016626). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51320. LOC89932 (Accession XM\_027341) is another

VGAM602 host target gene. LOC89932 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC89932, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC89932 BINDING SITE, designated SEQ ID:30485, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25550] Another function of VGAM602 is therefore inhibition of LOC89932 (Accession XM\_027341). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC89932. LOC90470 (Accession XM\_031975) is another VGAM602 host target gene. LOC90470 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90470, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90470 BINDING SITE, designated SEQ ID:31537, to the nucleotide sequence of VGAM602 RNA, herein designated VGAM RNA, also designated SEQ ID:3313.

[25551] Another function of VGAM602 is therefore inhibition of LOC90470 (Accession XM\_031975). Accordingly, utilities of VGAM602 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90470. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 603 (VGAM603) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25552] VGAM603 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM603 was detected is described hereinabove with reference to Figs. 1–8.

[25553] VGAM603 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM603 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25554] VGAM603 gene encodes a VGAM603 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM603

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM603 precursor RNA is designated SEQ ID:589, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:589 is located at position 11750 relative to the genome of Transmissible Gastroenteritis Virus.

[25555] VGAM603 precursor RNA folds onto itself, forming VGAM603 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25556] An enzyme complex designated DICER COMPLEX, `dices` the VGAM603 folded precursor RNA into VGAM603 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 42%) nucleotide sequence of VGAM603 RNA is designated SEQ ID:3314, and is provided hereinbelow with reference to the sequence listing part.

[25557] VGAM603 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM603 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM603 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[25558] VGAM603 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM603 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM603 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM603 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM603 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25559] The complementary binding of VGAM603 RNA, herein designated VGAM RNA, to host target binding sites on VGAM603 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM603 host target RNA into VGAM603 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25560] It is appreciated that VGAM603 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM603 host target genes. The mRNA of each one of this plurality of VGAM603 host target genes



comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM603 RNA, herein designated VGAM RNA, and which when bound by VGAM603 RNA causes inhibition of translation of respective one or more VGAM603 host target proteins.

[25561] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM603 gene, herein designated VGAM GENE, on one or more VGAM603 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25562] It is yet further appreciated that a function of VGAM603 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM603 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM603 correlate with, and may be deduced from, the identity of the host target genes which VGAM603 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25563] Nucleotide sequences of the VGAM603 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM603 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM603 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM603 are further described hereinbelow with reference to Table 1.

[25564] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM603 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM603 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[25565] As mentioned hereinabove with reference to Fig. 1, a function of VGAM603 gene, herein designated VGAM is inhibition of expression of VGAM603 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM603 correlate with, and may be deduced from, the identity of the target genes which VGAM603 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25566] Neural Precursor Cell Expressed, Developmentally Down-regulated 4-like (NEDD4L, Accession NM\_015277) is a VGAM603 host target gene. NEDD4L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEDD4L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEDD4L BINDING SITE, designated SEQ ID:17606, to the nucleotide sequence of VGAM603 RNA, herein designated VGAM RNA, also designated SEQ ID:3314.

[25567] A function of VGAM603 is therefore inhibition of Neural Precursor Cell Expressed, Developmentally Down-regulated 4-like (NEDD4L, Accession NM\_015277), a gene

which may play a role in the regulation of epithelial sodium channel function. Accordingly, utilities of VGAM603 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEDD4L. The function of NEDD4L has been established by previous studies. Using cosmids from a human chromosome 18-specific library, Chen et al. (2001) used exon trapping and cDNA cloning to identify a gene homologous to NEDD4. The full-length cDNA sequence of 3,246 bp, obtained by RACE, contains an open reading frame of 2,562 nucleotides. The deduced 854-amino acid polypeptide was predicted to contain 4 WW domains and an HECT ubiquitin-protein ligase domain, highly conserved features in the NEDD4 gene family. The NEDD4L gene has 97% and 62% amino acid sequence identity to mouse Nedd4-2 and human NEDD4 genes, respectively. By expression analysis, a 3.4-kb band was observed in heart and muscle, while a 3.2-kb band and/or an additional 3.6-kb band were seen in other tissues examined. An alternative splicing event involving exon 12 of 60 bp was observed, the shorter allele being predominantly present in brain and lymphocytes, while the longer allele was strongly expressed in kidney and placenta. Since the

NEDD4L gene mapped to the region of 18q21 showing linkage evidence for a susceptibility locus for bipolar affective disorder (OMIM Ref. No. 125480), Chen et al. (2001) screened the NEDD4L gene for mutations in 3 unrelated bipolar I probands and their parents, but no mutations were detected. Due to the potential role of NEDD4L in regulating the epithelial sodium channel (ENaC; OMIM Ref. No. 600228), Chen et al. (2001) proposed it a candidate gene for autosomal dominant orthostatic hypotensive disorder (OMIM Ref. No. 143850), mapped to 18q21. Erdenez and Rothstein (2000) found that the ubiquitination domain of KIAA0439 shares homology with the *S. cerevisiae* Rsp5, a ubiquitin-protein ligase. They analyzed Rsp5 mutant strains and concluded that Rsp5 may be involved in the degradation of the single-stranded DNA-binding protein Rfa1, thereby linking ubiquitin-dependent protein degradation to the replication-recombination machinery.

[25568] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25569] Chen, H.; Ross, C. A.; Wang, N.; Huo, Y.; MacKinnon, D. F.; Potash, J. B.; Simpson, S. G.; McMahon, F. J.; DePaulo, J. R.,

Jr.; McInnis, M. G. : NEDD4L on human chromosome 18q21 has multiple forms of transcripts and is a homologue of the mouse Nedd4-2 gene. *Europ. J. Hum. Genet.* 9: 922-930, 2001. ; and

[25570] Erdeniz, N.; Rothstein, R. : Rsp5, a ubiquitin-protein ligase, is involved in degradation of the single-stranded-DNA binding protein Rfa1 in *Saccharomyces cerevisiae*. *Molec. Cell. Bio.*

[25571] Further studies establishing the function and utilities of NEDD4L are found in John Hopkins OMIM database record ID 606384, and in cited publications numbered 6477-647 and 7555 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZp566D133 (Accession XM\_050005) is another VGAM603 host target gene. DKFZp566D133 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp566D133, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp566D133 BINDING SITE, designated SEQ ID:35546, to the nucleotide sequence of VGAM603 RNA, herein designated VGAM RNA, also designated SEQ ID:3314.

[25572] Another function of VGAM603 is therefore inhibition of DKFZp566D133 (Accession XM\_050005). Accordingly, utilities of VGAM603 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp566D133. Mitogen-activated Protein Kinase Kinase 6 (MAP2K6, Accession NM\_002758) is another VGAM603 host target gene. MAP2K6 BINDING SITE1 and MAP2K6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MAP2K6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP2K6 BINDING SITE1 and MAP2K6 BINDING SITE2, designated SEQ ID:8644 and SEQ ID:25703 respectively, to the nucleotide sequence of VGAM603 RNA, herein designated VGAM RNA, also designated SEQ ID:3314.

[25573] Another function of VGAM603 is therefore inhibition of Mitogen-activated Protein Kinase Kinase 6 (MAP2K6, Accession NM\_002758). Accordingly, utilities of VGAM603 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP2K6. LOC253959 (Accession XM\_170749) is another VGAM603

host target gene. LOC253959 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253959, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253959 BINDING SITE, designated SEQ ID:45512, to the nucleotide sequence of VGAM603 RNA, herein designated VGAM RNA, also designated SEQ ID:3314.

[25574] Another function of VGAM603 is therefore inhibition of LOC253959 (Accession XM\_170749). Accordingly, utilities of VGAM603 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253959. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 604 (VGAM604) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25575] VGAM604 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM604 was detected is described



hereinabove with reference to Figs. 1–8.

[25576] VGAM604 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM604 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25577] VGAM604 gene encodes a VGAM604 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM604 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM604 precursor RNA is designated SEQ ID:590, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:590 is located at position 9039 relative to the genome of Transmissible Gastroenteritis Virus.

[25578] VGAM604 precursor RNA folds onto itself, forming VGAM604 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25579] An enzyme complex designated DICER COMPLEX, `dices` the VGAM604 folded precursor RNA into VGAM604 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM604 RNA is designated SEQ ID:3315, and is provided hereinbelow with reference to the sequence listing part.

[25580] VGAM604 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM604 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM604 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25581] VGAM604 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM604 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM604 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM604 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM604 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25582] The complementary binding of VGAM604 RNA, herein designated VGAM RNA, to host target binding sites on VGAM604 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM604 host target RNA into VGAM604 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25583] It is appreciated that VGAM604 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM604 host target genes. The mRNA of each one of this plurality of VGAM604 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM604 RNA, herein designated VGAM RNA, and which when bound by VGAM604 RNA causes inhibition of translation of respective one or more VGAM604 host target proteins.

[25584] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM604 gene, herein designated VGAM GENE, on one or more VGAM604 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25585] It is yet further appreciated that a function of VGAM604 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM604 correlate with, and may be deduced from, the identity of the host target genes which VGAM604 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25586] Nucleotide sequences of the VGAM604 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM604 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM604 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM604 are further described hereinbelow with reference to Table 1.

[25587] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM604 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM604 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25588] As mentioned hereinabove with reference to Fig. 1, a function of VGAM604 gene, herein designated VGAM is inhibition of expression of VGAM604 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM604 correlate with, and may be deduced from, the identity of the target genes which VGAM604 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25589] Aspartoacylase (aminoacylase 2, Canavan disease) (ASPA, Accession NM\_000049) is a VGAM604 host target gene. ASPA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ASPA, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASPA BINDING SITE, designated SEQ ID:5489, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25590] A function of VGAM604 is therefore inhibition of Aspartoacylase (aminoacylase 2, Canavan disease) (ASPA, Accession NM\_000049). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASPA. Egl Nine Homolog 1 (C. elegans) (EGLN1, Accession NM\_022051) is another VGAM604 host target gene. EGLN1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EGLN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGLN1 BINDING SITE, designated SEQ ID:22588, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25591] Another function of VGAM604 is therefore inhibition of Egl Nine Homolog 1 (C. elegans) (EGLN1, Accession NM\_022051), a gene which is expressed in the cytoplasm

of arterial smooth muscle cells. Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN1. The function of EGLN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM216. Early Growth Response 3 (EGR3, Accession XM\_005040) is another VGAM604 host target gene. EGR3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGR3 BINDING SITE, designated SEQ ID:29960, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25592] Another function of VGAM604 is therefore inhibition of Early Growth Response 3 (EGR3, Accession XM\_005040), a gene which is a putative transcription factor. Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGR3. The function of EGR3 and its association with various diseases and clinical conditions, has been estab-



lished by previous studies, as described hereinabove with reference to VGAM189. Interferon (alpha, beta and omega) Receptor 2 (IFNAR2, Accession NM\_000874) is another VGAM604 host target gene. IFNAR2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by IFNAR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IFNAR2 BINDING SITE, designated SEQ ID:6551, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25593] Another function of VGAM604 is therefore inhibition of Interferon (alpha, beta and omega) Receptor 2 (IFNAR2, Accession NM\_000874), a gene which is a receptor for interferons alpha and beta. Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IFNAR2. The function of IFNAR2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM487. BAI1-associated Protein 1 (BAIAP1, Accession NM\_004742) is another VGAM604 host target gene. BA-

IAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BAIAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BAIAP1 BINDING SITE, designated SEQ ID:11138, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25594] Another function of VGAM604 is therefore inhibition of BAI1-associated Protein 1 (BAIAP1, Accession NM\_004742). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BAIAP1. DKFZp762K2015 (Accession XM\_051791) is another VGAM604 host target gene. DKFZp762K2015 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp762K2015, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762K2015 BINDING SITE, designated SEQ ID:35885, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM

RNA, also designated SEQ ID:3315.

[25595] Another function of VGAM604 is therefore inhibition of DKFZp762K2015 (Accession XM\_051791). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp762K2015. FLJ11127 (Accession NM\_019018) is another VGAM604 host target gene. FLJ11127 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11127, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11127 BINDING SITE, designated SEQ ID:21109, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25596] Another function of VGAM604 is therefore inhibition of FLJ11127 (Accession NM\_019018). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11127. KIAA0391 (Accession NM\_014672) is another VGAM604 host target gene. KIAA0391 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0391, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0391 BINDING SITE, designated SEQ ID:16138, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25597] Another function of VGAM604 is therefore inhibition of KIAA0391 (Accession NM\_014672). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0391. PAI-RBP1 (Accession NM\_015640) is another VGAM604 host target gene. PAI-RBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAI-RBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAI-RBP1 BINDING SITE, designated SEQ ID:17893, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25598] Another function of VGAM604 is therefore inhibition of PAI-RBP1 (Accession NM\_015640). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PAI-RBP1. SAD1 (Accession XM\_034123) is another VGAM604 host target gene. SAD1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SAD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SAD1 BINDING SITE, designated SEQ ID:32010, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25599] Another function of VGAM604 is therefore inhibition of SAD1 (Accession XM\_034123). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SAD1. LOC145868 (Accession XM\_096895) is another VGAM604 host target gene. LOC145868 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145868 BINDING SITE, designated SEQ ID:40620, to the nucleotide se-

quence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25600] Another function of VGAM604 is therefore inhibition of LOC145868 (Accession XM\_096895). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145868. LOC152316 (Accession XM\_098185) is another VGAM604 host target gene. LOC152316 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152316 BINDING SITE, designated SEQ ID:41454, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25601] Another function of VGAM604 is therefore inhibition of LOC152316 (Accession XM\_098185). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152316. LOC158230 (Accession XM\_088517) is another VGAM604 host target gene. LOC158230 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC158230, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158230 BINDING SITE, designated SEQ ID:39767, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25602] Another function of VGAM604 is therefore inhibition of LOC158230 (Accession XM\_088517). Accordingly, utilities of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158230. LOC91660 (Accession XM\_039902) is another VGAM604 host target gene. LOC91660 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91660, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91660 BINDING SITE, designated SEQ ID:33209, to the nucleotide sequence of VGAM604 RNA, herein designated VGAM RNA, also designated SEQ ID:3315.

[25603] Another function of VGAM604 is therefore inhibition of LOC91660 (Accession XM\_039902). Accordingly, utilities

of VGAM604 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91660. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 605 (VGAM605) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25604] VGAM605 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM605 was detected is described hereinabove with reference to Figs. 1–8.

[25605] VGAM605 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM605 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25606] VGAM605 gene encodes a VGAM605 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM605 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–



quence of VGAM605 precursor RNA is designated SEQ ID:591, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:591 is located at position 4344 relative to the genome of Transmissible Gastroenteritis Virus.

[25607] VGAM605 precursor RNA folds onto itself, forming VGAM605 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25608] An enzyme complex designated DICER COMPLEX, `dices` the VGAM605 folded precursor RNA into VGAM605 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM605 RNA is designated SEQ ID:3316, and

is provided hereinbelow with reference to the sequence listing part.

[25609] VGAM605 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM605 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM605 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25610] VGAM605 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM605 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM605 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM605 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM605 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25611] The complementary binding of VGAM605 RNA, herein designated VGAM RNA, to host target binding sites on VGAM605 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM605 host target RNA into VGAM605 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25612] It is appreciated that VGAM605 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM605 host target genes. The mRNA of each one of this plurality of VGAM605 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM605 RNA, herein designated VGAM RNA, and which when bound by VGAM605 RNA causes inhibition of translation of respective one or more VGAM605 host target proteins.

[25613] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM605 gene, herein designated VGAM GENE, on one or more VGAM605 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25614] It is yet further appreciated that a function of VGAM605 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM605 correlate with, and may be deduced from, the identity of the host target genes which VGAM605 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25615] Nucleotide sequences of the VGAM605 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM605 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM605 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM605 are further described hereinbelow with reference to Table 1.

[25616] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM605 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM605 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25617] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM605 gene, herein designated VGAM is inhibition of expression of VGAM605 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM605 correlate with, and may be deduced from, the identity of the target genes which VGAM605 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25618] Enabled Homolog (Drosophila) (ENAH, Accession NM\_018212) is a VGAM605 host target gene. ENAH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ENAH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ENAH BINDING SITE, designated SEQ ID:20121, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25619] A function of VGAM605 is therefore inhibition of Enabled Homolog (Drosophila) (ENAH, Accession NM\_018212). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ENAH. ERp44 (Accession XM\_088476) is another VGAM605 host target gene. ERp44 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ERp44, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ERp44 BINDING SITE, designated SEQ ID:39724, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25620] Another function of VGAM605 is therefore inhibition of ERp44 (Accession XM\_088476). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ERp44. MO25 (Accession NM\_016289) is another VGAM605 host target gene. MO25 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MO25, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MO25 BINDING SITE, designated SEQ ID:18415, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25621] Another function of VGAM605 is therefore inhibition of

MO25 (Accession NM\_016289). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MO25. LOC150372 (Accession XM\_086893) is another VGAM605 host target gene. LOC150372 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150372, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150372 BINDING SITE, designated SEQ ID:38935, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25622] Another function of VGAM605 is therefore inhibition of LOC150372 (Accession XM\_086893). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150372. LOC219940 (Accession XM\_167791) is another VGAM605 host target gene. LOC219940 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219940, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-



illustrates the complementarity of the nucleotide sequences of LOC219940 BINDING SITE, designated SEQ ID:44829, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25623] Another function of VGAM605 is therefore inhibition of LOC219940 (Accession XM\_167791). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219940. LOC222166 (Accession XM\_168425) is another VGAM605 host target gene. LOC222166 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222166 BINDING SITE, designated SEQ ID:45149, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25624] Another function of VGAM605 is therefore inhibition of LOC222166 (Accession XM\_168425). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222166. LOC51133 (Accession NM\_016121) is an-

other VGAM605 host target gene. LOC51133 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51133, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51133 BINDING SITE, designated SEQ ID:18203, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25625] Another function of VGAM605 is therefore inhibition of LOC51133 (Accession NM\_016121). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51133. LOC92181 (Accession XM\_043394) is another VGAM605 host target gene. LOC92181 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92181, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92181 BINDING SITE, designated SEQ ID:33943, to the nucleotide sequence of VGAM605 RNA, herein designated VGAM RNA, also designated SEQ ID:3316.

[25626] Another function of VGAM605 is therefore inhibition of LOC92181 (Accession XM\_043394). Accordingly, utilities of VGAM605 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92181. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 606 (VGAM606) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25627] VGAM606 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM606 was detected is described hereinabove with reference to Figs. 1–8.

[25628] VGAM606 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Transmissible Gastroenteritis Virus. VGAM606 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25629] VGAM606 gene encodes a VGAM606 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM606

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM606 precursor RNA is designated SEQ ID:592, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:592 is located at position 6033 relative to the genome of Transmissible Gastroenteritis Virus.

[25630] VGAM606 precursor RNA folds onto itself, forming VGAM606 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25631] An enzyme complex designated DICER COMPLEX, `dices` the VGAM606 folded precursor RNA into VGAM606 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 43%) nucleotide sequence of VGAM606 RNA is designated SEQ ID:3317, and is provided hereinbelow with reference to the sequence listing part.

[25632] VGAM606 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM606 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM606 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[25633] VGAM606 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM606 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM606 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM606 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM606 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25634] The complementary binding of VGAM606 RNA, herein designated VGAM RNA, to host target binding sites on VGAM606 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM606 host target RNA into VGAM606 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25635] It is appreciated that VGAM606 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM606 host target genes. The mRNA of each one of this plurality of VGAM606 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM606 RNA, herein designated VGAM RNA, and which when bound by VGAM606 RNA causes inhibition of translation of respective one or more VGAM606 host target proteins.

[25636] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM606 gene, herein designated VGAM GENE, on one or more VGAM606 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25637] It is yet further appreciated that a function of VGAM606 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of viral infection by Transmissible Gastroenteritis Virus. Specific functions, and accordingly utilities, of VGAM606 correlate with, and may be deduced from, the identity of the host target genes which VGAM606 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25638] Nucleotide sequences of the VGAM606 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM606 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM606 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM606 are further described hereinbelow with reference to Table 1.

[25639] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM606 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM606 RNA, herein designated VGAM RNA, are described hereinbelow with refer-



ence to Table 2.

[25640] As mentioned hereinabove with reference to Fig. 1, a function of VGAM606 gene, herein designated VGAM is inhibition of expression of VGAM606 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM606 correlate with, and may be deduced from, the identity of the target genes which VGAM606 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25641] Giant Axonal Neuropathy (gigaxonin) (GAN, Accession NM\_022041) is a VGAM606 host target gene. GAN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAN BINDING SITE, designated SEQ ID:22565, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25642] A function of VGAM606 is therefore inhibition of Giant Axonal Neuropathy (gigaxonin) (GAN, Accession NM\_022041), a gene which plays an important role in neurofilament architecture. Accordingly, utilities of

VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAN. The function of GAN has been established by previous studies. Giant axonal neuropathy (GAN; 256850), a severe autosomal recessive sensorineural neuropathy affecting both the peripheral nerves and the central nervous system, is characterized by neurofilament accumulation, leading to segmental distention of axons. The neuropathy is part of a generalized disorganization of the cytoskeletal intermediate filaments (IFs), to which neurofilaments belong, as abnormal aggregation of multiple tissue-specific IFs has been reported in this disorder: vimentin (VIM; 193060) in endothelial cells, Schwann cells, and cultured skin fibroblasts, and glial fibrillary acidic protein (GFAP; 137780) in astrocytes (Prineas et al., 1976; Pena, 1982; Bousquet et al., 1996). Keratin intermediate filaments also seem to be altered, as most patients present characteristic curly or kinky hairs (Treiber-Held et al., 1994). Bomont et al. (2000) used a positional cloning approach to isolate a novel, ubiquitously expressed gene that encoded a protein they named gigaxonin and contained mutations associated with giant axonal neuropathy. Gigaxonin contains an N-terminal BTB (broad-complex, tramtrack, and bric-

a-brac) domain followed by 6 kelch repeats, which were predicted to adopt a beta-propeller shape. Distantly related proteins sharing a similar domain organization have various functions associated with the cytoskeleton, predicting that gigaxonin is a novel and distinct cytoskeletal protein that may represent a general pathologic target for other neurodegenerative disorders with alterations in the neurofilament network.

[25643] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25644] Bomont, P.; Cavalier, L.; Blondeau, F.; Ben Hamida, C.; Belal, S.; Tazir, M.; Demir, E.; Topaloglu, H.; Korinthenberg, R.; Tuysuz, B.; Landrieu, P.; Hentati, F.; Koenig, M. : The gene encoding gigaxonin, a new member of the cytoskeletal BTB/kelch repeat family, is mutated in giant axonal neuropathy. *Nature Genet.* 26: 370–374, 2000. ; and

[25645] Bousquet, O.; Basseville, M.; Vila-Porcile, E.; Billette de Villemeur, T.; Hauw, J.-J.; Landrieu, P.; Portier, M.-M. : Aggregation of a subpopulation of vimentin filaments in cultured.

[25646] Further studies establishing the function and utilities of GAN are found in John Hopkins OMIM database record ID

605379, and in cited publications numbered 9215–698 and 9216 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Glutaminase (GLS, Accession NM\_014905) is another VGAM606 host target gene. GLS BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GLS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLS BINDING SITE, designated SEQ ID:17113, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25647] Another function of VGAM606 is therefore inhibition of Glutaminase (GLS, Accession NM\_014905). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLS. HUS1 Checkpoint Homolog (*S. pombe*) (HUS1, Accession XM\_165873) is another VGAM606 host target gene. HUS1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HUS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-

ble 2 illustrates the complementarity of the nucleotide sequences of HUS1 BINDING SITE, designated SEQ ID:43791, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25648] Another function of VGAM606 is therefore inhibition of HUS1 Checkpoint Homolog (*S. pombe*) (HUS1, Accession XM\_165873), a gene which May form DNA damage-responsive protein complex . Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUS1. The function of HUS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM228. Interleukin 20 Receptor, Alpha (IL20RA, Accession NM\_014432) is another VGAM606 host target gene. IL20RA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL20RA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL20RA BINDING SITE, designated SEQ ID:15790, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ

ID:3317.

[25649] Another function of VGAM606 is therefore inhibition of Interleukin 20 Receptor, Alpha (IL20RA, Accession NM\_014432), a gene which is the receptor for interleukin-20. Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL20RA. The function of IL20RA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM315. Plastin 1 (I isoform) (PLS1, Accession NM\_002670) is another VGAM606 host target gene. PLS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLS1 BINDING SITE, designated SEQ ID:8539, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25650] Another function of VGAM606 is therefore inhibition of Plastin 1 (I isoform) (PLS1, Accession NM\_002670). Accordingly, utilities of VGAM606 include diagnosis, preven-

tion and treatment of diseases and clinical conditions associated with PLS1. Chromosome 1 Open Reading Frame 17 (C1orf17, Accession XM\_042965) is another VGAM606 host target gene. C1orf17 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C1orf17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1orf17 BINDING SITE, designated SEQ ID:33851, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25651] Another function of VGAM606 is therefore inhibition of Chromosome 1 Open Reading Frame 17 (C1orf17, Accession XM\_042965). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf17. KIAA0894 (Accession NM\_014896) is another VGAM606 host target gene. KIAA0894 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of KIAA0894 BINDING SITE, designated SEQ ID:17061, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25652] Another function of VGAM606 is therefore inhibition of KIAA0894 (Accession NM\_014896). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0894. KIAA1181 (Accession XM\_043340) is another VGAM606 host target gene. KIAA1181 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1181, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1181 BINDING SITE, designated SEQ ID:33925, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25653] Another function of VGAM606 is therefore inhibition of KIAA1181 (Accession XM\_043340). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1181. Neural Precursor Cell Expressed, Developmen-



tally Down-regulated 5 (NEDD5, Accession NM\_004404) is another VGAM606 host target gene. NEDD5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NEDD5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEDD5 BINDING SITE, designated SEQ ID:10659, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25654] Another function of VGAM606 is therefore inhibition of Neural Precursor Cell Expressed, Developmentally Down-regulated 5 (NEDD5, Accession NM\_004404). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEDD5. LOC154525 (Accession XM\_098554) is another VGAM606 host target gene. LOC154525 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC154525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154525 BINDING SITE, designated SEQ ID:41709, to

the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25655] Another function of VGAM606 is therefore inhibition of LOC154525 (Accession XM\_098554). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154525. LOC221271 (Accession XM\_166307) is another VGAM606 host target gene. LOC221271 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221271, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221271 BINDING SITE, designated SEQ ID:44127, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25656] Another function of VGAM606 is therefore inhibition of LOC221271 (Accession XM\_166307). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221271. LOC253260 (Accession XM\_171097) is another VGAM606 host target gene. LOC253260 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC253260, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253260 BINDING SITE, designated SEQ ID:45910, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25657] Another function of VGAM606 is therefore inhibition of LOC253260 (Accession XM\_171097). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253260. LOC90841 (Accession XM\_034427) is another VGAM606 host target gene. LOC90841 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90841, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90841 BINDING SITE, designated SEQ ID:32115, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25658] Another function of VGAM606 is therefore inhibition of LOC90841 (Accession XM\_034427). Accordingly, utilities

of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90841. LOC91149 (Accession XM\_036480) is another VGAM606 host target gene. LOC91149 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91149, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91149 BINDING SITE, designated SEQ ID:32461, to the nucleotide sequence of VGAM606 RNA, herein designated VGAM RNA, also designated SEQ ID:3317.

[25659] Another function of VGAM606 is therefore inhibition of LOC91149 (Accession XM\_036480). Accordingly, utilities of VGAM606 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91149. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 607 (VGAM607) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25660] VGAM607 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM607 was detected is described hereinabove with reference to Figs. 1–8.

[25661] VGAM607 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rice Grassy Stunt Virus. VGAM607 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25662] VGAM607 gene encodes a VGAM607 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM607 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM607 precursor RNA is designated SEQ ID:593, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:593 is located at position 8963 relative to the genome of Rice Grassy Stunt Virus.

[25663] VGAM607 precursor RNA folds onto itself, forming VGAM607 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

‘hairpin structure’, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[25664] An enzyme complex designated DICER COMPLEX, ‘dices’ the VGAM607 folded precursor RNA into VGAM607 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, ‘dicing’ of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 48%) nucleotide sequence of VGAM607 RNA is designated SEQ ID:3318, and is provided hereinbelow with reference to the sequence listing part.

[25665] VGAM607 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM607 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM607 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5’ untranslated region, a protein coding region and a 3’ untranslated region, designated 5’UTR, PROTEIN

CODING and 3`UTR respectively.

[25666] VGAM607 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM607 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM607 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM607 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM607 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25667] The complementary binding of VGAM607 RNA, herein designated VGAM RNA, to host target binding sites on VGAM607 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM607 host target RNA into VGAM607 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25668] It is appreciated that VGAM607 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM607 host target genes. The mRNA of each one of this plurality of VGAM607 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM607 RNA, herein designated VGAM RNA, and which when bound by VGAM607 RNA causes inhibition of translation of respective one or more VGAM607 host target proteins.

[25669] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM607 gene, herein designated VGAM GENE, on one or more VGAM607 host target gene, herein designated



VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25670] It is yet further appreciated that a function of VGAM607 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM607 include diagnosis, prevention and treatment of viral infection by Rice Grassy Stunt Virus. Specific functions, and accordingly utilities, of VGAM607 correlate with, and may be deduced from, the identity of the host target genes which VGAM607 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25671] Nucleotide sequences of the VGAM607 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM607 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM607 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM607 are further  
described hereinbelow with reference to Table 1.

[25672] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM607 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM607 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[25673] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM607 gene, herein designated VGAM is  
inhibition of expression of VGAM607 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM607 correlate with, and may be deduced  
from, the identity of the target genes which VGAM607  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[25674] Parathyroid Hormone Receptor 2 (PTH2, Accession  
NM\_005048) is a VGAM607 host target gene. PTH2

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTHR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTHR2 BINDING SITE, designated SEQ ID:11481, to the nucleotide sequence of VGAM607 RNA, herein designated VGAM RNA, also designated SEQ ID:3318.

[25675] A function of VGAM607 is therefore inhibition of Parathyroid Hormone Receptor 2 (PTHR2, Accession NM\_005048), a gene which is a G protein-coupled receptor selective for parathyroid hormone binding. Accordingly, utilities of VGAM607 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTHR2. The function of PTHR2 has been established by previous studies. Usdin et al. (1995) identified a 7-transmembrane-domain G protein-coupled receptor that selectively recognizes parathyroid hormone (PTH; 168450). The receptor, which they designated PTHR2, is a member of the secretin receptor family of G protein-coupled receptors (see OMIM Ref. No. 182098). There is 30 to 70% amino acid sequence identity between receptors within the secretin receptor family, but these receptors

have essentially no sequence identity with most known G protein-coupled receptors of the rhodopsin family (see OMIM Ref. No. 180380) or with the metabotropic glutamate receptor family (see OMIM Ref. No. 601115). PTHR2 is most similar (51% overall amino acid identity) to the PTH/PTHrP receptor (OMIM Ref. No. 168468). The PTHR2 gene was most abundantly expressed in brain, pancreas, testis, and placenta. Although both PTH and PTH-related peptide (PTHrP; 168470) bind to the PTH/PTHrP receptor and stimulate cAMP accumulation with similar efficacy, only PTH activates PTHR2. To determine the structural basis for this selectivity, Clark et al. (1998) analyzed receptor chimeras in which the amino terminus and third extracellular domains of the 2 receptors were interchanged. Simultaneous interchange of wildtype amino termini and third extracellular loops eliminated agonist activation but not binding for both receptors. These results suggested that the amino terminus and third extracellular loop of the PTH2 and PTH/PTHrP receptors interact similarly with PTH, and that both domains contribute to differential interaction with PTHrP.

[25676] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [25677] Usdin, T. B.; Gruber, C.; Bonner, T. I. : Identification and functional expression of a receptor selectively recognizing parathyroid hormone, the PTH2 receptor. J. Biol. Chem. 270: 15455–15458, 1995. ; and
- [25678] Clark, J. A.; Bonner, T. I.; Kim, A. S.; Usdin, T. B. : Multiple regions of ligand discrimination revealed by analysis of chimeric parathyroid hormone 2 (PTH2) and PTH/PTH-related peptid.
- [25679] Further studies establishing the function and utilities of PTHR2 are found in John Hopkins OMIM database record ID 601469, and in cited publications numbered 6691–6693 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ23017 (Accession NM\_022840) is another VGAM607 host target gene. FLJ23017 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23017 BINDING SITE, designated SEQ ID:23129, to the nucleotide sequence of VGAM607 RNA, herein designated VGAM RNA, also designated SEQ

ID:3318.

[25680] Another function of VGAM607 is therefore inhibition of FLJ23017 (Accession NM\_022840). Accordingly, utilities of VGAM607 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23017. KIAA1622 (Accession NM\_058237) is another VGAM607 host target gene. KIAA1622 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1622, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1622 BINDING SITE, designated SEQ ID:27767, to the nucleotide sequence of VGAM607 RNA, herein designated VGAM RNA, also designated SEQ ID:3318.

[25681] Another function of VGAM607 is therefore inhibition of KIAA1622 (Accession NM\_058237). Accordingly, utilities of VGAM607 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1622. LOC145820 (Accession XM\_085246) is another VGAM607 host target gene. LOC145820 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145820, corresponding

to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145820 BINDING SITE, designated SEQ ID:37987, to the nucleotide sequence of VGAM607 RNA, herein designated VGAM RNA, also designated SEQ ID:3318.

[25682] Another function of VGAM607 is therefore inhibition of LOC145820 (Accession XM\_085246). Accordingly, utilities of VGAM607 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145820. LOC149420 (Accession XM\_086530) is another VGAM607 host target gene. LOC149420 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149420 BINDING SITE, designated SEQ ID:38748, to the nucleotide sequence of VGAM607 RNA, herein designated VGAM RNA, also designated SEQ ID:3318.

[25683] Another function of VGAM607 is therefore inhibition of LOC149420 (Accession XM\_086530). Accordingly, utilities of VGAM607 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC149420. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 608 (VGAM608) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25684] VGAM608 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM608 was detected is described hereinabove with reference to Figs. 1–8.

[25685] VGAM608 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rice Grass Stunt Virus. VGAM608 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25686] VGAM608 gene encodes a VGAM608 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM608 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM608 precursor RNA is designated SEQ



ID:594, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:594 is located at position 1950 relative to the genome of Rice Grassy Stunt Virus.

[25687] VGAM608 precursor RNA folds onto itself, forming VGAM608 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25688] An enzyme complex designated DICER COMPLEX, `dices` the VGAM608 folded precursor RNA into VGAM608 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM608 RNA is designated SEQ ID:3319, and is provided hereinbelow with reference to the sequence

listing part.

[25689] VGAM608 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM608 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM608 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25690] VGAM608 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM608 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM608 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM608 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM608 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25691] The complementary binding of VGAM608 RNA, herein designated VGAM RNA, to host target binding sites on VGAM608 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM608 host target RNA into VGAM608 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25692] It is appreciated that VGAM608 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM608 host target genes. The mRNA of each one of this plurality of VGAM608 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM608 RNA, herein designated VGAM

RNA, and which when bound by VGAM608 RNA causes inhibition of translation of respective one or more VGAM608 host target proteins.

[25693] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM608 gene, herein designated VGAM GENE, on one or more VGAM608 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25694] It is yet further appreciated that a function of VGAM608 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM608 include diagnosis, prevention and treatment of viral infection by Rice Grassy Stunt Virus. Specific functions, and accordingly utilities, of VGAM608 correlate with, and may be deduced from, the identity of the host target genes which VGAM608 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25695] Nucleotide sequences of the VGAM608 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM608 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM608 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM608 are further described hereinbelow with reference to Table 1.

[25696] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM608 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM608 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25697] As mentioned hereinabove with reference to Fig. 1, a function of VGAM608 gene, herein designated VGAM is

inhibition of expression of VGAM608 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM608 correlate with, and may be deduced from, the identity of the target genes which VGAM608 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25698] A Disintegrin and Metalloproteinase Domain 28 (ADAM28, Accession NM\_014265) is a VGAM608 host target gene. ADAM28 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAM28, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM28 BINDING SITE, designated SEQ ID:15541, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25699] A function of VGAM608 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 28 (ADAM28, Accession NM\_014265), a gene which Member of the MDC family of metalloproteinases. Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM28.

The function of ADAM28 has been established by previous studies. ADAM28 belongs to a family of cell surface and secreted glycoproteins that possess both proteolytic and adhesive properties (Bridges et al., 2002). ADAM proteins have been implicated in neurogenesis, fertilization, muscle development, and the release of membrane-anchored proteins. By PCR with degenerate primers on lymph node cDNA, searching sequence databases, and probing a lymph node cDNA library, Roberts et al. (1999) isolated cDNAs encoding 2 splice variants of ADAM28, which they designated MDCL. The deduced 775-amino acid trans-membrane variant, MDCLm, has the typical ADAM domain structure, including signal peptide, propeptide, metallo-protease, disintegrin, cysteine-rich, EGF, and transmembrane domains. The deduced 540-amino acid secreted variant, MDCLs, has signal peptide, propeptide, metallo-protease, and disintegrin domains identical to those of MDCLm; however, its cysteine-rich domain differs in sequence and contains a stop codon midway through. In addition, MDCLm has 6 potential N-linked glycosylation sites, while MDCLs has only 3. Northern blot and RT-PCR analyses revealed expression of a 2.8-kb MDCLm transcript in spleen, lymph node, and, to a lesser extent, in

peripheral blood leukocytes. MDCLs was primarily expressed in spleen as a 2.2-kb transcript. Immunoblot analysis of peripheral blood lymphocytes recognized MDCL proteins of 87 and 67 kD. Immunohistochemical analysis detected expression of MDCL in multiple T- and B-lymphocyte-containing tissues. Jury et al. (1999) cloned ADAM28, which they termed eMDC II, from macaque and human epididymis.

[25700] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25701] Bridges, L. C.; Tani, P. H.; Hanson, K. R.; Roberts, C. M.; Judkins, M. B.; Bowditch, R. D. : The lymphocyte metalloprotease MDC-L (ADAM28) is a ligand for the integrin  $\alpha$ -4/ $\beta$ -1. J. Biol. Chem. 277: 3784-3792, 2002. ; and

[25702] Roberts, C. M.; Tani, P. H.; Bridges, L. C.; Laszik, Z.; Bowditch, R. D. : MDC-L, a novel metalloprotease disintegrin cysteine-rich protein family member expressed by human lymphocytes.

[25703] Further studies establishing the function and utilities of ADAM28 are found in John Hopkins OMIM database record ID 606188, and in cited publications numbered



6132–6135 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Collagen, Type IV, Alpha 3 (Goodpasture antigen) (COL4A3, Accession NM\_031363) is another VGAM608 host target gene. COL4A3 BINDING SITE1 through COL4A3 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by COL4A3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COL4A3 BINDING SITE1 through COL4A3 BINDING SITE3, designated SEQ ID:25354, SEQ ID:25360 and SEQ ID:5547 respectively, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25704] Another function of VGAM608 is therefore inhibition of Collagen, Type IV, Alpha 3 (Goodpasture antigen) (COL4A3, Accession NM\_031363). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COL4A3. Dihydropyrimidinase-like 2 (DPYSL2, Accession NM\_001386) is another VGAM608 host target gene. DPYSL2 BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by DPYSL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DPYSL2 BINDING SITE, designated SEQ ID:7066, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25705] Another function of VGAM608 is therefore inhibition of Dihydropyrimidinase-like 2 (DPYSL2, Accession NM\_001386), a gene which is a member of the dihydropyrimidinase family. Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DPYSL2. The function of DPYSL2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM217.DXS1283E (Accession XM\_047871) is another VGAM608 host target gene. DXS1283E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DXS1283E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of DXS1283E BINDING SITE, designated SEQ ID:35064, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25706] Another function of VGAM608 is therefore inhibition of DXS1283E (Accession XM\_047871). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DXS1283E. Epithelial Membrane Protein 1 (EMP1, Accession NM\_001423) is another VGAM608 host target gene. EMP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EMP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EMP1 BINDING SITE, designated SEQ ID:7131, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25707] Another function of VGAM608 is therefore inhibition of Epithelial Membrane Protein 1 (EMP1, Accession NM\_001423), a gene which plays a role in squamous cell differentiation; member of the PMP22/EMP/MP20 family of membrane glycoproteins. Accordingly, utilities of

VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EMP1. The function of EMP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM107. Ficolin (collagen/fibrinogen domain containing) 3 (Hakata antigen) (FCN3, Accession NM\_003665) is another VGAM608 host target gene. FCN3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FCN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FCN3 BINDING SITE, designated SEQ ID:9744, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25708] Another function of VGAM608 is therefore inhibition of Ficolin (collagen/fibrinogen domain containing) 3 (Hakata antigen) (FCN3, Accession NM\_003665). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FCN3. Glutaminase (GLS, Accession NM\_014905) is another VGAM608 host target gene. GLS BINDING SITE is

HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GLS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLS BINDING SITE, designated SEQ ID:17111, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25709] Another function of VGAM608 is therefore inhibition of Glutaminase (GLS, Accession NM\_014905). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLS. Leucine Zipper Transcription Factor-like 1 (LZTFL1, Accession NM\_020347) is another VGAM608 host target gene. LZTFL1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LZTFL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LZTFL1 BINDING SITE, designated SEQ ID:21601, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25710] Another function of VGAM608 is therefore inhibition of Leucine Zipper Transcription Factor-like 1 (LZTFL1, Accession NM\_020347). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LZTFL1. Protease, Serine, 16 (thymus) (PRSS16, Accession NM\_005865) is another VGAM608 host target gene. PRSS16 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRSS16, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRSS16 BINDING SITE, designated SEQ ID:12482, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25711] Another function of VGAM608 is therefore inhibition of Protease, Serine, 16 (thymus) (PRSS16, Accession NM\_005865). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRSS16. Solute Carrier Family 20 (phosphate transporter), Member 1 (SLC20A1, Accession XM\_002217) is another VGAM608 host target gene. SLC20A1 BINDING SITE is HOST TARGET binding site

found in the 5' untranslated region of mRNA encoded by SLC20A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC20A1 BINDING SITE, designated SEQ ID:29874, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25712] Another function of VGAM608 is therefore inhibition of Solute Carrier Family 20 (phosphate transporter), Member 1 (SLC20A1, Accession XM\_002217), a gene which could be a sodium-phosphate symporter. Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC20A1. The function of SLC20A1 has been established by previous studies. By expression in *Xenopus* oocytes and in mammalian cells, Kavanaugh et al. (1994) determined that GLVR1 is a sodium-dependent phosphate symporter. Voltage-clamp analysis indicated net cation influx, suggesting that phosphate is transported with excess sodium ions. Palmer et al. (1999) showed that the GLVR1 gene consists of 11 exons spanning approximately 18 kb of genomic DNA. Exon 1 is noncoding. Using a lu-

ciferase reporter gene assay in transiently transfected chondrocytes and osteoblasts, Palmer et al. (2001) determined that the activity of the promoter of SLC20A1, which they called PIT1, requires a TATA-like sequence and a single SP1 (OMIM Ref. No. 189906) site. They found that this SP1 site could bind SP1 and SP3 (OMIM Ref. No. 601804). Despite the conservation of sequence between the human and mouse promoter, the promoter of mouse Pit1 depends on a combination of several cis-acting elements.

[25713] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25714] Kavanaugh, M. P.; Miller, D. G.; Zhang, W.; Law, W.; Kozak, S. L.; Kabat, D.; Miller, A. D. : Cell-surface receptors for gibbon ape leukemia virus and amphotropic murine retrovirus are inducible sodium-dependent phosphate symporters. Proc. Nat. Acad. Sci. 91: 7071-7075, 1994. ; and

[25715] Palmer, G.; Manen, D.; Bonjour, J.-P.; Caverzasio, J. : Species-specific mechanisms control the activity of the Pit1/PIT1 phosphate transporter gene promoter in mouse and human. Gene 279.

[25716] Further studies establishing the function and utilities of



SLC20A1 are found in John Hopkins OMIM database record ID 137570, and in cited publications numbered 4026–402 and 4007 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tripartite Motif-containing 9 (TRIM9, Accession NM\_015163) is another VGAM608 host target gene. TRIM9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM9 BINDING SITE, designated SEQ ID:17514, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25717] Another function of VGAM608 is therefore inhibition of Tripartite Motif-containing 9 (TRIM9, Accession NM\_015163), a gene which may function as a positive regulator for mannosylphosphate transferase and is required to mediate mannosylphosphate transfer in both the core and outer chain portions of n-linked oligosaccharides. Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM9. The function of TRIM9 and

its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74. Zinc Finger Protein 215 (ZNF215, Accession NM\_013250) is another VGAM608 host target gene. ZNF215 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZNF215, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF215 BINDING SITE, designated SEQ ID:14912, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25718] Another function of VGAM608 is therefore inhibition of Zinc Finger Protein 215 (ZNF215, Accession NM\_013250). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF215. Apolipoprotein A-V (APOA5, Accession NM\_052968) is another VGAM608 host target gene. APOA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APOA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of APOA5 BINDING SITE, designated SEQ ID:27540, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25719] Another function of VGAM608 is therefore inhibition of Apolipoprotein A-V (APOA5, Accession NM\_052968). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOA5. Rho GTPase Activating Protein 5 (ARHGAP5, Accession XM\_085082) is another VGAM608 host target gene. ARHGAP5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGAP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP5 BINDING SITE, designated SEQ ID:37821, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25720] Another function of VGAM608 is therefore inhibition of Rho GTPase Activating Protein 5 (ARHGAP5, Accession XM\_085082). Accordingly, utilities of VGAM608 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP5. Rho Guanine Nucleotide Exchange Factor (GEF) 4 (ARHGEF4, Accession NM\_032995) is another VGAM608 host target gene.

ARHGEF4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGEF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGEF4 BINDING SITE, designated SEQ ID:26875, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25721] Another function of VGAM608 is therefore inhibition of Rho Guanine Nucleotide Exchange Factor (GEF) 4 (ARHGEF4, Accession NM\_032995). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGEF4. ARNTL2 (Accession NM\_020183) is another VGAM608 host target gene. ARNTL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARNTL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARNTL2 BINDING SITE, designated SEQ ID:21421, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25722] Another function of VGAM608 is therefore inhibition of ARNTL2 (Accession NM\_020183). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARNTL2. DKFZP727G051 (Accession XM\_045308) is another VGAM608 host target gene. DKFZP727G051 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP727G051, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP727G051 BINDING SITE, designated SEQ ID:34431, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25723] Another function of VGAM608 is therefore inhibition of DKFZP727G051 (Accession XM\_045308). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with DKFZP727G051. DKFZp761D221 (Accession NM\_032291) is another VGAM608 host target gene. DKFZp761D221 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp761D221, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761D221 BINDING SITE, designated SEQ ID:26058, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25724] Another function of VGAM608 is therefore inhibition of DKFZp761D221 (Accession NM\_032291). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761D221. FLJ10687 (Accession NM\_018178) is another VGAM608 host target gene. FLJ10687 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10687 BINDING SITE, designated SEQ ID:20012, to the

nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25725] Another function of VGAM608 is therefore inhibition of FLJ10687 (Accession NM\_018178). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10687. FLJ13855 (Accession NM\_023079) is another VGAM608 host target gene. FLJ13855 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13855, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13855 BINDING SITE, designated SEQ ID:23345, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25726] Another function of VGAM608 is therefore inhibition of FLJ13855 (Accession NM\_023079). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13855. FLJ20006 (Accession NM\_017618) is another VGAM608 host target gene. FLJ20006 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ20006, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20006 BINDING SITE, designated SEQ ID:19119, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25727] Another function of VGAM608 is therefore inhibition of FLJ20006 (Accession NM\_017618). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20006. FLJ20986 (Accession NM\_024524) is another VGAM608 host target gene. FLJ20986 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20986, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20986 BINDING SITE, designated SEQ ID:23728, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25728] Another function of VGAM608 is therefore inhibition of FLJ20986 (Accession NM\_024524). Accordingly, utilities of



VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20986. KIAA0907 (Accession NM\_014949) is another VGAM608 host target gene. KIAA0907 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0907, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0907 BINDING SITE, designated SEQ ID:17277, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25729] Another function of VGAM608 is therefore inhibition of KIAA0907 (Accession NM\_014949). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0907. moblak (Accession NM\_130807) is another VGAM608 host target gene. moblak BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by moblak, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of moblak BINDING

SITE, designated SEQ ID:28312, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25730] Another function of VGAM608 is therefore inhibition of moblak (Accession NM\_130807). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with moblak. PA26 (Accession NM\_014454) is another VGAM608 host target gene. PA26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PA26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PA26 BINDING SITE, designated SEQ ID:15809, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25731] Another function of VGAM608 is therefore inhibition of PA26 (Accession NM\_014454). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PA26. PRO2730 (Accession NM\_025222) is another VGAM608 host target gene. PRO2730 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by PRO2730, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2730 BINDING SITE, designated SEQ ID:24900, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25732] Another function of VGAM608 is therefore inhibition of PRO2730 (Accession NM\_025222). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2730. SSH2 (Accession XM\_030846) is another VGAM608 host target gene. SSH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSH2 BINDING SITE, designated SEQ ID:31187, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25733] Another function of VGAM608 is therefore inhibition of

SSH2 (Accession XM\_030846). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSH2. STAF65(gamma) (Accession NM\_014860) is another VGAM608 host target gene. STAF65(gamma) BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by STAF65(gamma), corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAF65(gamma) BINDING SITE, designated SEQ ID:16927, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25734] Another function of VGAM608 is therefore inhibition of STAF65(gamma) (Accession NM\_014860). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAF65(gamma). SZF1 (Accession NM\_016089) is another VGAM608 host target gene. SZF1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SZF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of SZF1 BINDING SITE, designated SEQ ID:18176, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25735] Another function of VGAM608 is therefore inhibition of SZF1 (Accession NM\_016089). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SZF1. LOC134637 (Accession XM\_059727) is another VGAM608 host target gene. LOC134637 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC134637, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC134637 BINDING SITE, designated SEQ ID:37078, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25736] Another function of VGAM608 is therefore inhibition of LOC134637 (Accession XM\_059727). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC134637. LOC136345 (Accession XM\_072455) is an-

other VGAM608 host target gene. LOC136345 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC136345, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC136345 BINDING SITE, designated SEQ ID:37502, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25737] Another function of VGAM608 is therefore inhibition of LOC136345 (Accession XM\_072455). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC136345. LOC147694 (Accession XM\_085843) is another VGAM608 host target gene. LOC147694 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147694, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147694 BINDING SITE, designated SEQ ID:38373, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25738] Another function of VGAM608 is therefore inhibition of LOC147694 (Accession XM\_085843). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147694. LOC155032 (Accession XM\_098647) is another VGAM608 host target gene. LOC155032 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC155032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155032 BINDING SITE, designated SEQ ID:41750, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25739] Another function of VGAM608 is therefore inhibition of LOC155032 (Accession XM\_098647). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155032. LOC158835 (Accession XM\_088683) is another VGAM608 host target gene. LOC158835 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158835, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158835 BINDING SITE, designated SEQ ID:39897, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25740] Another function of VGAM608 is therefore inhibition of LOC158835 (Accession XM\_088683). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158835. LOC199991 (Accession XM\_117169) is another VGAM608 host target gene. LOC199991 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC199991, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199991 BINDING SITE, designated SEQ ID:43276, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25741] Another function of VGAM608 is therefore inhibition of LOC199991 (Accession XM\_117169). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC199991. LOC255520 (Accession XM\_171073) is another VGAM608 host target gene. LOC255520 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255520, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255520 BINDING SITE, designated SEQ ID:45880, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25742] Another function of VGAM608 is therefore inhibition of LOC255520 (Accession XM\_171073). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255520. LOC257358 (Accession XM\_173138) is another VGAM608 host target gene. LOC257358 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257358, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257358 BINDING SITE, designated SEQ ID:46391, to the nucleotide sequence of VGAM608 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3319.

[25743] Another function of VGAM608 is therefore inhibition of LOC257358 (Accession XM\_173138). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257358. LOC90485 (Accession XM\_032059) is another VGAM608 host target gene. LOC90485 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90485, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90485 BINDING SITE, designated SEQ ID:31556, to the nucleotide sequence of VGAM608 RNA, herein designated VGAM RNA, also designated SEQ ID:3319.

[25744] Another function of VGAM608 is therefore inhibition of LOC90485 (Accession XM\_032059). Accordingly, utilities of VGAM608 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90485. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 609 (VGAM609) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25745] VGAM609 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM609 was detected is described hereinabove with reference to Figs. 1–8.

[25746] VGAM609 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rice Grassy Stunt Virus. VGAM609 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25747] VGAM609 gene encodes a VGAM609 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM609 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM609 precursor RNA is designated SEQ ID:595, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:595 is located at position 8205 relative to the genome of Rice Grassy Stunt Virus.

[25748] VGAM609 precursor RNA folds onto itself, forming

VGAM609 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25749] An enzyme complex designated DICER COMPLEX, `dices` the VGAM609 folded precursor RNA into VGAM609 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 58%) nucleotide sequence of VGAM609 RNA is designated SEQ ID:3320, and is provided hereinbelow with reference to the sequence listing part.

[25750] VGAM609 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM609 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM609 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25751] VGAM609 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM609 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM609 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM609 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM609 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25752] The complementary binding of VGAM609 RNA, herein designated VGAM RNA, to host target binding sites on VGAM609 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM609 host target RNA into VGAM609 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25753] It is appreciated that VGAM609 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM609 host target genes. The mRNA of each one of this plurality of VGAM609 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM609 RNA, herein designated VGAM RNA, and which when bound by VGAM609 RNA causes inhibition of translation of respective one or more VGAM609 host target proteins.

[25754] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM609 gene, herein designated VGAM GENE, on one or more VGAM609 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25755] It is yet further appreciated that a function of VGAM609 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of viral infection by Rice Grass Stunt Virus. Specific functions, and accordingly utilities, of VGAM609 correlate with, and may be deduced from, the identity of the host target genes which VGAM609 binds and inhibits,

and the function of these host target genes, as elaborated hereinbelow.

[25756] Nucleotide sequences of the VGAM609 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM609 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM609 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM609 are further described hereinbelow with reference to Table 1.

[25757] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM609 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM609 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25758] As mentioned hereinabove with reference to Fig. 1, a function of VGAM609 gene, herein designated VGAM is inhibition of expression of VGAM609 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM609 correlate with, and may be deduced from, the identity of the target genes which VGAM609 binds and inhibits, and the function of these target genes,



as elaborated hereinbelow.

[25759] Adrenergic, Alpha-2B-, Receptor (ADRA2B, Accession NM\_000682) is a VGAM609 host target gene. ADRA2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADRA2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADRA2B BINDING SITE, designated SEQ ID:6340, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25760] A function of VGAM609 is therefore inhibition of Adrenergic, Alpha-2B-, Receptor (ADRA2B, Accession NM\_000682), a gene which mediate the catecholamine-induced inhibition of adenylate cyclase through the action of g proteins. Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADRA2B. The function of ADRA2B has been established by previous studies. Regan et al. (1988) indicated that in addition to the platelet alpha-2-adrenergic receptor (ADRA2A, encoded by chromosome 10; 104210) and the renal form of receptor

(ADRA2C, encoded by chromosome 4; 104250), a related protein is coded by chromosome 2. Lomasney et al. (1990) also cloned the ADRA2B gene. By hybridization with somatic cell hybrids, they showed that the gene for this receptor is located on chromosome 2. Northern blot analysis of various rat tissues showed expression in liver and kidney. Unique pharmacology and tissue localization suggested that this was a previously unidentified subtype. Alpha-2-adrenergic receptors have a critical role in regulating neurotransmitter release from sympathetic nerves and from adrenergic neurons in the central nervous system. To help elucidate the individual roles of the 3 highly homologous alpha-2-adrenergic receptors (ADRA2A, ADRA2B, and ADRA2C) in this process, Hein et al. (1999) studied neurotransmitter release in mice in which the genes encoding the 3 alpha-2-adrenergic-receptor subtypes were disrupted. By PCR-SSCP analysis, Heinonen et al. (1999) screened the entire coding sequence of the ADRA2B gene in 58 obese, nondiabetic Finns. They identified a polymorphism that led to a deletion of 3 glutamic acids from a glutamic acid repeat element (glu12, amino acids 297 to 309) present in the third intracellular loop of the receptor protein. This repeat element had been shown

to be important for agonist-dependent receptor desensitization.

[25761] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25762] Lomasney, J. W.; Lorenz, W.; Allen, L. F.; King, K.; Regan, J. W.; Yang-Feng, T. L.; Caron, M. G.; Lefkowitz, R. J. : Expansion of the alpha-2-adrenergic receptor family: cloning and characterization of a human alpha-2-adrenergic receptor subtype, the gene for which is located on chromosome 2. Proc. Nat. Acad. Sci. 87: 5094-5098, 1990. ; and

[25763] Heinonen, P.; Koulu, M.; Pesonen, U.; Karvonen, M. K.; Rissanen, A.; Laakso, M.; Valve, R.; Uusitupa, M.; Scheinin, M. : Identification of a three-amino acid deletion in the alpha-2B-adr.

[25764] Further studies establishing the function and utilities of ADRA2B are found in John Hopkins OMIM database record ID 104260, and in cited publications numbered 12106-48 and 478 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CD8 Antigen, Alpha Polypeptide (p32) (CD8A, Accession NM\_001768) is another VGAM609 host target gene. CD8A

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CD8A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD8A BINDING SITE, designated SEQ ID:7530, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25765] Another function of VGAM609 is therefore inhibition of CD8 Antigen, Alpha Polypeptide (p32) (CD8A, Accession NM\_001768), a gene which is thought to play a role in the process of t-cell mediated killing. Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD8A. The function of CD8A has been established by previous studies. Comparative structural and functional studies of mouse and human T-cell antigens showed that human cytotoxic-suppressor T cells have a molecule homologous to the mouse Lyt-2,Lyt-3 molecule (Ledbetter et al., 1981). The human homolog of Lyt-2,Lyt-3 is termed LEU2. It is selectively expressed on a subset of T cells and in structure is a multimeric macromolecule composed of individual disulfide-bonded subunits. LEU2, or T8, is ex-

pressed by most T lymphocytes with cytotoxic or suppressor function. The molecule appears to be composed of multimers of a 32-kD and a 45-kD polypeptide in thymocytes and of a 32-kD polypeptide in peripheral blood lymphocytes. LEU2 (like its proposed murine homolog Lyt-2) may play a role in target-cell recognition. Kavathas et al. (1984) isolated genomic and cDNA clones for LEU2. Gibling et al. (1989) showed that through alternative splicing of mRNA, an exon encoding a transmembrane domain of CD8 is deleted. This gives rise to a 30-kD molecule that is secreted and exists as a monomer. The splicing pattern in man differs from that found in the mouse CD8 gene. This mRNA is also alternatively spliced, but an exon encoding a cytoplasmic region is deleted, giving rise to a cell surface molecule that differs in its cytoplasmic tail from the protein encoded by the longer mRNA. Neither protein is secreted. This is an example of the different splicing patterns of 2 homologous mouse and human genes giving rise to different proteins. This represents 1 mechanism of generating diversity during speciation Animal model experiments lend further support to the function of CD8A. Leishman et al. (2001) used tetramer analysis in a mouse model to show that thymus leukemia anti-

gen (TL; 188850), which is expressed abundantly on intestinal epithelial cells, preferentially binds to the homotypic form of CD8A (CD8A–CD8A), in contrast to other major histocompatibility complex molecules that bind to CD8A–CD8B (OMIM Ref. No. 186730). Flow cytometric analysis demonstrated that most intestinal intraepithelial lymphocytes (IELs), but not splenocytes, react specifically to TL tetramers. Leishman et al. (2001) concluded that CD8A–CD8A on IELs acts semiautonomously, rather than as a T-cell receptor coreceptor. They suggested that expression of CD8A–CD8A on IELs could have important regulatory effects that influence homeostasis, activation, and survival of IELs under the high antigen load of the intestine

[25766] It is appreciated that the abovementioned animal model for CD8A is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[25767] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25768] Kavathas, P.; Sukhatme, V. P.; Herzenberg, L. A.; Parnes, J. R. : Isolation of the gene encoding the human T–

lymphocyte differentiation antigen Leu-2 (T8) by gene transfer and cDNA subtraction. Proc. Nat. Acad. Sci. 81: 7688-7692, 1984. ; and

[25769] Leishman, A. J.; Naidenko, O. V.; Attinger, A.; Koning, F.; Lena, C. J.; Xiong, Y.; Chang, H.-C.; Reinherz, E.; Kronenberg, M.; Cheroutre, H. : T cell responses modulated through interac.

[25770] Further studies establishing the function and utilities of CD8A are found in John Hopkins OMIM database record ID 186910, and in cited publications numbered 6028-6039, 605 and 9776-9778 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ20509 (Accession NM\_017851) is another VGAM609 host target gene. FLJ20509 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20509, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20509 BINDING SITE, designated SEQ ID:19522, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25771] Another function of VGAM609 is therefore inhibition of

FLJ20509 (Accession NM\_017851). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20509. FLJ21777 (Accession NM\_032209) is another VGAM609 host target gene. FLJ21777 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21777, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21777 BINDING SITE, designated SEQ ID:25924, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25772] Another function of VGAM609 is therefore inhibition of FLJ21777 (Accession NM\_032209). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21777. KIAA1586 (Accession XM\_166451) is another VGAM609 host target gene. KIAA1586 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1586, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of KIAA1586 BINDING SITE, designated SEQ ID:44349, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25773] Another function of VGAM609 is therefore inhibition of KIAA1586 (Accession XM\_166451). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1586. KIAA1841 (Accession XM\_087056) is another VGAM609 host target gene. KIAA1841 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1841, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1841 BINDING SITE, designated SEQ ID:39026, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25774] Another function of VGAM609 is therefore inhibition of KIAA1841 (Accession XM\_087056). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1841. MGC30052 (Accession NM\_144721) is another

VGAM609 host target gene. MGC30052 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC30052, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC30052 BINDING SITE, designated SEQ ID:29545, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25775] Another function of VGAM609 is therefore inhibition of MGC30052 (Accession NM\_144721). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC30052. N-myristoyltransferase 1 (NMT1, Accession NM\_021079) is another VGAM609 host target gene. NMT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NMT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NMT1 BINDING SITE, designated SEQ ID:22049, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25776] Another function of VGAM609 is therefore inhibition of N-myristoyltransferase 1 (NMT1, Accession NM\_021079). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NMT1. Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230) is another VGAM609 host target gene. NUDT11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUDT11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUDT11 BINDING SITE, designated SEQ ID:30143, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25777] Another function of VGAM609 is therefore inhibition of Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUDT11. P5-1 (Accession NM\_006674) is another VGAM609 host target gene. P5-1 BINDING SITE is HOST

TARGET binding site found in the 3` untranslated region of mRNA encoded by P5-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P5-1 BINDING SITE, designated SEQ ID:13496, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25778] Another function of VGAM609 is therefore inhibition of P5-1 (Accession NM\_006674). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P5-1. Synaptotagmin XIII (SYT13, Accession XM\_167880) is another VGAM609 host target gene. SYT13 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SYT13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYT13 BINDING SITE, designated SEQ ID:44887, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25779] Another function of VGAM609 is therefore inhibition of

Synaptotagmin XIII (SYT13, Accession XM\_167880). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYT13. LOC130813 (Accession XM\_065904) is another VGAM609 host target gene. LOC130813 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130813, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130813 BINDING SITE, designated SEQ ID:37313, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25780] Another function of VGAM609 is therefore inhibition of LOC130813 (Accession XM\_065904). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130813. LOC157681 (Accession XM\_088363) is another VGAM609 host target gene. LOC157681 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157681, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC157681 BINDING SITE, designated SEQ ID:39641, to the nucleotide sequence of VGAM609 RNA, herein designated VGAM RNA, also designated SEQ ID:3320.

[25781] Another function of VGAM609 is therefore inhibition of LOC157681 (Accession XM\_088363). Accordingly, utilities of VGAM609 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157681. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 610 (VGAM610) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25782] VGAM610 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM610 was detected is described hereinabove with reference to Figs. 1–8.

[25783] VGAM610 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rice Grass Stunt Virus. VGAM610 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[25784] VGAM610 gene encodes a VGAM610 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM610 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM610 precursor RNA is designated SEQ ID:596, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:596 is located at position 4515 relative to the genome of Rice Grassy Stunt Virus.

[25785] VGAM610 precursor RNA folds onto itself, forming VGAM610 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25786] An enzyme complex designated DICER COMPLEX, `dices` the VGAM610 folded precursor RNA into VGAM610 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM610 RNA is designated SEQ ID:3321, and is provided hereinbelow with reference to the sequence listing part.

[25787] VGAM610 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM610 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM610 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25788] VGAM610 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM610 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM610 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-



quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM610 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM610 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25789] The complementary binding of VGAM610 RNA, herein designated VGAM RNA, to host target binding sites on VGAM610 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM610 host target RNA into VGAM610 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25790] It is appreciated that VGAM610 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM610 host target genes. The mRNA of each one of this plurality of VGAM610 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM610 RNA, herein designated VGAM RNA, and which when bound by VGAM610 RNA causes inhibition of translation of respective one or more VGAM610 host target proteins.

[25791] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM610 gene, herein designated VGAM GENE, on one or more VGAM610 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25792] It is yet further appreciated that a function of VGAM610 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM610 include diagnosis, prevention and treatment of viral infection by Rice Grass Stunt Virus. Specific functions, and accordingly utilities, of VGAM610 correlate with, and may be deduced from, the identity of the host target genes which VGAM610 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25793] Nucleotide sequences of the VGAM610 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM610 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM610 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM610 are further described hereinbelow with reference to Table 1.

[25794] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM610 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM610 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25795] As mentioned hereinabove with reference to Fig. 1, a function of VGAM610 gene, herein designated VGAM is inhibition of expression of VGAM610 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM610 correlate with, and may be deduced from, the identity of the target genes which VGAM610 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25796] Tumor Necrosis Factor Receptor Superfamily, Member 6b, Decoy (TNFRSF6B, Accession NM\_016434) is a VGAM610 host target gene. TNFRSF6B BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TNFRSF6B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFRSF6B BINDING SITE, designated SEQ ID:18557, to the nucleotide sequence of VGAM610 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3321.

[25797] A function of VGAM610 is therefore inhibition of Tumor Necrosis Factor Receptor Superfamily, Member 6b, Decoy (TNFRSF6B, Accession NM\_016434), a gene which is decoy receptor and protects against apoptosis. Accordingly, utilities of VGAM610 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFRSF6B. The function of TNFRSF6B has been established by previous studies. Pitti et al. (1998) identified ESTs that showed homology to the tumor necrosis factor receptor (TNFR) superfamily. Using PCR with primers based on the region of EST consensus, they isolated a cDNA encoding a soluble decoy receptor, termed decoy receptor-3 (DCR3), from a human fetal lung cDNA library. The DCR3 protein contains 300 amino acids and has a molecular mass of 35 kD. By Northern blot analysis, Pitti et al. (1998) detected a 1.2-kb transcript in human fetal lung, brain, and liver, and in adult spleen, colon, and lung. Pitti et al. (1998) demonstrated that DCR3 binds to FASL and inhibits FASL-induced apoptosis. Like osteoprotegerin (OPG; 602643), another TNFR superfamily member, DCR3 lacks an apparent transmembrane sequence, indicating that DCR3 may be a secreted, rather than a membrane-

associated, molecule. The DCR3 protein shares 31% sequence homology with OPG, and all of the cysteines in the 4 cysteine-rich domains of DCR3 and OPG are conserved. Pitti et al. (1998) stated that DCR3 and OPG define a subset of TNFR family members that function as secreted decoys to modulate ligands that induce apoptosis. Bai et al. (2000) independently identified the DCR3 gene, which they called M68. M68 genomic DNA, mRNA, and protein levels were examined in a series of human gastrointestinal tract tumors. Using M68 immunohistochemistry and a scoring system similar to that used for HER-2/neu (ERBB2; 164870), they found that M68 protein was overexpressed in 30 of 68 (44%) human adenocarcinomas of the esophagus, stomach, colon, and rectum. Tumors examined by Northern blot revealed M68 mRNA highly elevated in a similar fraction of primary tumors from the same gastrointestinal tract regions, as well as in 2 colon adenocarcinoma cell lines. They also found M68 protein to be overexpressed in a substantial number of tumors in which gene amplification could not be detected by fluorescence in situ hybridization or quantitative genomic PCR, suggesting that overexpression of M68 may precede amplification in tumors. They found that M68 lies within a

4-gene cluster that includes a novel helicase-like gene related to RAD3/ERCC2 (OMIM Ref. No. 126340), a plasma membrane Ras-related GTPase and a member of the stathmin family (OMIM Ref. No. 151442), amplification or overexpression of which may also contribute to cell growth and tumor progression.

[25798] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25799] Bai, C.; Connolly, B.; Metzker, M. L.; Hilliard, C. A.; Liu, X.; Sandig, V.; Soderman, A.; Galloway, S. M.; Liu, Q.; Austin, C. P.; Caskey, C. T. : Overexpression of M68/DCR3 in human gastrointestinal tract tumors independent of gene amplification and its location in a four-gene cluster. Proc. Nat. Acad. Sci. 97: 1230–1235, 2000. ; and

[25800] Pitti, R. M.; Marsters, S. A.; Lawrence, D. A.; Roy, M.; Kischkel, F. C.; Dowd, P.; Huang, A.; Donahue, C. J.; Sherwood, S. W.; Baldwin, D. T.; Godowski, P. J.; Wood, W. I.; Gurney, A.

[25801] Further studies establishing the function and utilities of TNFRSF6B are found in John Hopkins OMIM database record ID 603361, and in cited publications numbered 8657–8658 listed in the bibliography section hereinbelow,

which are also hereby incorporated by reference. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 611 (VGAM611) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25802] VGAM611 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM611 was detected is described hereinabove with reference to Figs. 1–8.

[25803] VGAM611 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Xestia C-nigrum Granulovirus. VGAM611 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25804] VGAM611 gene encodes a VGAM611 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM611 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM611 precursor RNA is designated SEQ ID:597, and is provided hereinbelow with reference to the



sequence listing part. Nucleotide sequence SEQ ID:597 is located at position 62972 relative to the genome of Xestia C-nigrum Granulovirus.

[25805] VGAM611 precursor RNA folds onto itself, forming VGAM611 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25806] An enzyme complex designated DICER COMPLEX, `dices` the VGAM611 folded precursor RNA into VGAM611 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM611 RNA is designated SEQ ID:3322, and is provided hereinbelow with reference to the sequence listing part.

[25807] VGAM611 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM611 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM611 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25808] VGAM611 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM611 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM611 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM611 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM611 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[25809] The complementary binding of VGAM611 RNA, herein designated VGAM RNA, to host target binding sites on VGAM611 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM611 host target RNA into VGAM611 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25810] It is appreciated that VGAM611 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM611 host target genes. The mRNA of each one of this plurality of VGAM611 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM611 RNA, herein designated VGAM RNA, and which when bound by VGAM611 RNA causes in-

hibition of translation of respective one or more VGAM611 host target proteins.

[25811] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM611 gene, herein designated VGAM GENE, on one or more VGAM611 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25812] It is yet further appreciated that a function of VGAM611 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM611 include diagnosis, prevention and

treatment of viral infection by Xestia C-nigrum Granulovirus. Specific functions, and accordingly utilities, of VGAM611 correlate with, and may be deduced from, the identity of the host target genes which VGAM611 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25813] Nucleotide sequences of the VGAM611 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM611 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM611 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM611 are further described hereinbelow with reference to Table 1.

[25814] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM611 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM611 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25815] As mentioned hereinabove with reference to Fig. 1, a function of VGAM611 gene, herein designated VGAM is inhibition of expression of VGAM611 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM611 correlate with, and may be deduced from, the identity of the target genes which VGAM611 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25816] Agmatine Ureohydrolase (agmatinase) (AGMAT, Accession NM\_024758) is a VGAM611 host target gene. AGMAT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AGMAT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AGMAT BINDING SITE, designated SEQ ID:24106, to the nucleotide sequence of VGAM611 RNA, herein designated VGAM RNA, also designated SEQ ID:3322.

[25817] A function of VGAM611 is therefore inhibition of Agmatine Ureohydrolase (agmatinase) (AGMAT, Accession NM\_024758). Accordingly, utilities of VGAM611 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AGMAT. KIAA0337 (Accession NM\_014786) is another VGAM611 host target gene. KIAA0337 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by KIAA0337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0337 BINDING SITE, designated SEQ ID:16654, to the nucleotide sequence of VGAM611 RNA, herein designated VGAM RNA, also designated SEQ ID:3322.

[25818] Another function of VGAM611 is therefore inhibition of KIAA0337 (Accession NM\_014786). Accordingly, utilities of VGAM611 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0337. KIAA0544 (Accession XM\_048119) is another VGAM611 host target gene. KIAA0544 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0544, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0544 BINDING SITE, designated SEQ ID:35110, to the nucleotide sequence of VGAM611 RNA, herein designated VGAM RNA, also designated SEQ ID:3322.

[25819] Another function of VGAM611 is therefore inhibition of KIAA0544 (Accession XM\_048119). Accordingly, utilities

of VGAM611 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0544. KIAA0825 (Accession XM\_027906) is another VGAM611 host target gene. KIAA0825 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0825, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0825 BINDING SITE, designated SEQ ID:30590, to the nucleotide sequence of VGAM611 RNA, herein designated VGAM RNA, also designated SEQ ID:3322.

[25820] Another function of VGAM611 is therefore inhibition of KIAA0825 (Accession XM\_027906). Accordingly, utilities of VGAM611 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0825. Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654) is another VGAM611 host target gene. SDC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of



SDC3 BINDING SITE, designated SEQ ID:16078, to the nucleotide sequence of VGAM611 RNA, herein designated VGAM RNA, also designated SEQ ID:3322.

[25821] Another function of VGAM611 is therefore inhibition of Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654). Accordingly, utilities of VGAM611 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDC3. LOC51301 (Accession NM\_016591) is another VGAM611 host target gene. LOC51301 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51301 BINDING SITE, designated SEQ ID:18671, to the nucleotide sequence of VGAM611 RNA, herein designated VGAM RNA, also designated SEQ ID:3322.

[25822] Another function of VGAM611 is therefore inhibition of LOC51301 (Accession NM\_016591). Accordingly, utilities of VGAM611 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51301. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 612 (VGAM612) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25823] VGAM612 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM612 was detected is described hereinabove with reference to Figs. 1–8.

[25824] VGAM612 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Xestia C-nigrum Granulovirus. VGAM612 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25825] VGAM612 gene encodes a VGAM612 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM612 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM612 precursor RNA is designated SEQ ID:598, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:598 is located at position 72787 relative to the genome of Xestia

C-nigrum Granulovirus.

[25826] VGAM612 precursor RNA folds onto itself, forming VGAM612 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25827] An enzyme complex designated DICER COMPLEX, `dices` the VGAM612 folded precursor RNA into VGAM612 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM612 RNA is designated SEQ ID:3323, and is provided hereinbelow with reference to the sequence listing part.

[25828] VGAM612 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM612 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM612 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25829] VGAM612 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM612 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM612 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM612 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM612 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25830] The complementary binding of VGAM612 RNA, herein designated VGAM RNA, to host target binding sites on VGAM612 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM612 host target RNA into VGAM612 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25831] It is appreciated that VGAM612 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM612 host target genes. The mRNA of each one of this plurality of VGAM612 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM612 RNA, herein designated VGAM RNA, and which when bound by VGAM612 RNA causes inhibition of translation of respective one or more VGAM612 host target proteins.

[25832] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM612 gene, herein designated VGAM GENE, on one or more VGAM612 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25833] It is yet further appreciated that a function of VGAM612 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM612 include diagnosis, prevention and treatment of viral infection by Xestia C-nigrum Granulovirus. Specific functions, and accordingly utilities, of

VGAM612 correlate with, and may be deduced from, the identity of the host target genes which VGAM612 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25834] Nucleotide sequences of the VGAM612 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM612 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM612 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM612 are further described hereinbelow with reference to Table 1.

[25835] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM612 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM612 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25836] As mentioned hereinabove with reference to Fig. 1, a function of VGAM612 gene, herein designated VGAM is inhibition of expression of VGAM612 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM612 correlate with, and may be deduced

from, the identity of the target genes which VGAM612 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25837] Epithelial V-like Antigen 1 (EVA1, Accession NM\_005797) is a VGAM612 host target gene. EVA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EVA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVA1 BINDING SITE, designated SEQ ID:12379, to the nucleotide sequence of VGAM612 RNA, herein designated VGAM RNA, also designated SEQ ID:3323.

[25838] A function of VGAM612 is therefore inhibition of Epithelial V-like Antigen 1 (EVA1, Accession NM\_005797). Accordingly, utilities of VGAM612 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EVA1. DKFZp434E0519 (Accession NM\_032247) is another VGAM612 host target gene. DKFZp434E0519 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp434E0519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING



SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434E0519 BINDING SITE, designated SEQ ID:25983, to the nucleotide sequence of VGAM612 RNA, herein designated VGAM RNA, also designated SEQ ID:3323.

[25839] Another function of VGAM612 is therefore inhibition of DKFZp434E0519 (Accession NM\_032247). Accordingly, utilities of VGAM612 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434E0519. LOC148166 (Accession XM\_086077) is another VGAM612 host target gene. LOC148166 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148166 BINDING SITE, designated SEQ ID:38480, to the nucleotide sequence of VGAM612 RNA, herein designated VGAM RNA, also designated SEQ ID:3323.

[25840] Another function of VGAM612 is therefore inhibition of LOC148166 (Accession XM\_086077). Accordingly, utilities of VGAM612 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC148166. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 613 (VGAM613) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25841] VGAM613 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM613 was detected is described hereinabove with reference to Figs. 1–8.

[25842] VGAM613 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Xestia C-nigrum Granulovirus. VGAM613 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25843] VGAM613 gene encodes a VGAM613 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM613 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM613 precursor RNA is designated SEQ

ID:599, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:599 is located at position 74562 relative to the genome of Xestia C-nigrum Granulovirus.

[25844] VGAM613 precursor RNA folds onto itself, forming VGAM613 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25845] An enzyme complex designated DICER COMPLEX, `dices` the VGAM613 folded precursor RNA into VGAM613 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM613 RNA is designated SEQ ID:3324, and is provided hereinbelow with reference to the sequence

listing part.

[25846] VGAM613 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM613 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM613 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25847] VGAM613 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM613 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM613 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM613 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM613 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25848] The complementary binding of VGAM613 RNA, herein designated VGAM RNA, to host target binding sites on VGAM613 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM613 host target RNA into VGAM613 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25849] It is appreciated that VGAM613 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM613 host target genes. The mRNA of each one of this plurality of VGAM613 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM613 RNA, herein designated VGAM

RNA, and which when bound by VGAM613 RNA causes inhibition of translation of respective one or more VGAM613 host target proteins.

[25850] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM613 gene, herein designated VGAM GENE, on one or more VGAM613 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25851] It is yet further appreciated that a function of VGAM613 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM613 include diagnosis, prevention and treatment of viral infection by Xestia C-nigrum Granulovirus. Specific functions, and accordingly utilities, of VGAM613 correlate with, and may be deduced from, the identity of the host target genes which VGAM613 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25852] Nucleotide sequences of the VGAM613 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM613 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM613 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM613 are further described hereinbelow with reference to Table 1.

[25853] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM613 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM613 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25854] As mentioned hereinabove with reference to Fig. 1, a function of VGAM613 gene, herein designated VGAM is

inhibition of expression of VGAM613 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM613 correlate with, and may be deduced from, the identity of the target genes which VGAM613 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25855] Chromosome 20 Open Reading Frame 7 (C20orf7, Accession NM\_024120) is a VGAM613 host target gene. C20orf7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf7 BINDING SITE, designated SEQ ID:23571, to the nucleotide sequence of VGAM613 RNA, herein designated VGAM RNA, also designated SEQ ID:3324.

[25856] A function of VGAM613 is therefore inhibition of Chromosome 20 Open Reading Frame 7 (C20orf7, Accession NM\_024120). Accordingly, utilities of VGAM613 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf7. Eukaryotic Translation Initiation Factor 3, Subunit 1 Alpha, 35kDa (EIF3S1,



Accession XM\_032384) is another VGAM613 host target gene. EIF3S1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF3S1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF3S1 BINDING SITE, designated SEQ ID:31641, to the nucleotide sequence of VGAM613 RNA, herein designated VGAM RNA, also designated SEQ ID:3324.

[25857] Another function of VGAM613 is therefore inhibition of Eukaryotic Translation Initiation Factor 3, Subunit 1 Alpha, 35kDa (EIF3S1, Accession XM\_032384). Accordingly, utilities of VGAM613 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF3S1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 614 (VGAM614) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25858] VGAM614 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM614 was detected is described hereinabove with reference to Figs. 1–8.

[25859] VGAM614 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Xestia C–nigrum Granulovirus. VGAM614 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25860] VGAM614 gene encodes a VGAM614 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM614 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM614 precursor RNA is designated SEQ ID:600, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:600 is located at position 74778 relative to the genome of Xestia C–nigrum Granulovirus.

[25861] VGAM614 precursor RNA folds onto itself, forming VGAM614 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two–dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25862] An enzyme complex designated DICER COMPLEX, `dices` the VGAM614 folded precursor RNA into VGAM614 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM614 RNA is designated SEQ ID:3325, and is provided hereinbelow with reference to the sequence listing part.

[25863] VGAM614 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM614 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM614 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25864] VGAM614 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM614 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM614 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM614 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM614 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25865] The complementary binding of VGAM614 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM614 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM614 host target RNA into VGAM614 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25866] It is appreciated that VGAM614 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM614 host target genes. The mRNA of each one of this plurality of VGAM614 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM614 RNA, herein designated VGAM RNA, and which when bound by VGAM614 RNA causes inhibition of translation of respective one or more VGAM614 host target proteins.

[25867] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM614 gene, herein designated VGAM GENE, on one or more VGAM614 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25868] It is yet further appreciated that a function of VGAM614 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM614 include diagnosis, prevention and treatment of viral infection by Xestia C-nigrum Granulovirus. Specific functions, and accordingly utilities, of VGAM614 correlate with, and may be deduced from, the identity of the host target genes which VGAM614 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25869] Nucleotide sequences of the VGAM614 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM614 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM614 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM614 are further described hereinbelow with reference to Table 1.

[25870] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM614 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM614 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25871] As mentioned hereinabove with reference to Fig. 1, a function of VGAM614 gene, herein designated VGAM is inhibition of expression of VGAM614 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM614 correlate with, and may be deduced from, the identity of the target genes which VGAM614 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25872] Cytochrome B-245, Beta Polypeptide (chronic granulomatous disease) (CYBB, Accession XM\_084288) is a VGAM614 host target gene. CYBB BINDING SITE is HOST TARGET

binding site found in the 3` untranslated region of mRNA encoded by CYBB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYBB BINDING SITE, designated SEQ ID:37536, to the nucleotide sequence of VGAM614 RNA, herein designated VGAM RNA, also designated SEQ ID:3325.

[25873] A function of VGAM614 is therefore inhibition of Cytochrome B-245, Beta Polypeptide (chronic granulomatous disease) (CYBB, Accession XM\_084288). Accordingly, utilities of VGAM614 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYBB. HSPC155 (Accession NM\_016406) is another VGAM614 host target gene. HSPC155 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by HSPC155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC155 BINDING SITE, designated SEQ ID:18539, to the nucleotide sequence of VGAM614 RNA, herein designated VGAM RNA, also designated SEQ ID:3325.



[25874] Another function of VGAM614 is therefore inhibition of HSPC155 (Accession NM\_016406). Accordingly, utilities of VGAM614 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC155. LOC158431 (Accession XM\_098940) is another VGAM614 host target gene. LOC158431 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158431, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158431 BINDING SITE, designated SEQ ID:41991, to the nucleotide sequence of VGAM614 RNA, herein designated VGAM RNA, also designated SEQ ID:3325.

[25875] Another function of VGAM614 is therefore inhibition of LOC158431 (Accession XM\_098940). Accordingly, utilities of VGAM614 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158431. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 615 (VGAM615) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[25876] VGAM615 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM615 was detected is described hereinabove with reference to Figs. 1–8.

[25877] VGAM615 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Xestia C-nigrum Granulovirus. VGAM615 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25878] VGAM615 gene encodes a VGAM615 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM615 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM615 precursor RNA is designated SEQ ID:601, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:601 is located at position 128621 relative to the genome of Xestia C-nigrum Granulovirus.

[25879] VGAM615 precursor RNA folds onto itself, forming VGAM615 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[25880] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM615 folded precursor RNA into VGAM615 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 41%) nucleotide se-  
quence of VGAM615 RNA is designated SEQ ID:3326, and  
is provided hereinbelow with reference to the sequence  
listing part.

[25881] VGAM615 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM615 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM615 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25882] VGAM615 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM615 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM615 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM615 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM615 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25883] The complementary binding of VGAM615 RNA, herein designated VGAM RNA, to host target binding sites on VGAM615 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM615 host target RNA into VGAM615 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25884] It is appreciated that VGAM615 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM615 host target genes. The mRNA of each one of this plurality of VGAM615 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM615 RNA, herein designated VGAM RNA, and which when bound by VGAM615 RNA causes inhibition of translation of respective one or more VGAM615 host target proteins.

[25885] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM615 gene, herein designated VGAM GENE, on one or more VGAM615 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25886] It is yet further appreciated that a function of VGAM615 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of viral infection by Xestia C-nigrum Granulovirus. Specific functions, and accordingly utilities, of VGAM615 correlate with, and may be deduced from, the identity of the host target genes which VGAM615 binds and inhibits, and the function of these host target genes,

as elaborated hereinbelow.

[25887] Nucleotide sequences of the VGAM615 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM615 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM615 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM615 are further described hereinbelow with reference to Table 1.

[25888] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM615 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM615 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25889] As mentioned hereinabove with reference to Fig. 1, a function of VGAM615 gene, herein designated VGAM is inhibition of expression of VGAM615 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM615 correlate with, and may be deduced from, the identity of the target genes which VGAM615 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25890] Axin 1 (AXIN1, Accession XM\_027520) is a VGAM615 host target gene. AXIN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AXIN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AXIN1 BINDING SITE, designated SEQ ID:30514, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25891] A function of VGAM615 is therefore inhibition of Axin 1 (AXIN1, Accession XM\_027520). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AXIN1. EGF-like-domain, Multiple 4 (EGFL4, Accession XM\_029883) is another VGAM615 host target gene. EGFL4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGFL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGFL4 BINDING SITE, designated SEQ ID:30965, to the nucleotide sequence of VGAM615 RNA, herein designated



VGAM RNA, also designated SEQ ID:3326.

[25892] Another function of VGAM615 is therefore inhibition of EGF-like-domain, Multiple 4 (EGFL4, Accession XM\_029883). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGFL4. Formin-like (FMNL, Accession NM\_005892) is another VGAM615 host target gene. FMNL BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FMNL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FMNL BINDING SITE, designated SEQ ID:12512, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25893] Another function of VGAM615 is therefore inhibition of Formin-like (FMNL, Accession NM\_005892), a gene which controls the reorganization of the actin cytoskeleton in association with Rac. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FMNL. The function of FMNL has been established by previous studies. By sequencing a recombinant cosmid library, Aronsson et al.

(1998) identified 2 genes, NIK (OMIM Ref. No. 604655) and C17ORF1B. Northern blot analysis revealed that C17ORF1B is expressed as a 1.8-kb transcript in heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas. By directed sequencing of the cosmid library, Aronsson et al. (1998) showed that C17ORF1B contains 11 exons spanning 5.1 kb of genomic DNA. Yayoshi-Yamamoto et al. (2000) isolated cDNAs encoding mouse Frl-alpha and Frl-beta (formin-related gene in leukocytes) that appeared to be homologs of C17ORF1B. Western blot, immunofluorescence, and Northern blot analyses showed that Frl is expressed as a 160-kD cytosolic protein that is highly expressed in spleen, lymph node, and bone marrow cells and that it associates with Rac (see OMIM Ref. No. 602048) and profilin (see OMIM Ref. No. 176610). Yayoshi-Yamamoto et al. (2000) suggested that Frl may play a role in the control of reorganization of the actin cytoskeleton in association with Rac and in the regulation of the signal for cell survival. By FISH and radiation hybrid analysis, Aronsson et al. (1998) mapped the C17ORF1B gene to chromosome 17q21. Using exon-intron maps and mutation screening, Aronsson et al. (1998) found no disease-specific alterations in the C17ORF1B gene in a pedi-

gree with frontotemporal dementia and parkinsonism linked to chromosome 17 (OMIM Ref. No. 600274).

[25894] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25895] Aronsson, F. C.; Magnusson, P.; Andersson, B.; Karsten, S. L.; Shibasaki, Y.; Lendon, C. L.; Goate, A. M.; Brookes, A. J. : The NIK protein kinase and C17orf1 genes: chromosomal mapping, gene structures and mutational screening in frontotemporal dementia and parkinsonism linked to chromosome 17. Hum. Genet. 103: 340–345, 1998. ; and

[25896] Yayoshi–Yamamoto, S.; Taniuchi, I.; Watanabe, T. : FRL, a novel formin–related protein, binds to Rac and regulates cell motility and survival of macrophages. Molec. Cell. Biol. 20: 6872.

[25897] Further studies establishing the function and utilities of FMNL are found in John Hopkins OMIM database record ID 604656, and in cited publications numbered 7284–7285 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Farnesyltransferase, CAAX Box, Beta (FNTB, Accession NM\_002028) is another VGAM615 host target gene. FNTB BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by FNTB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FNTB BINDING SITE, designated SEQ ID:7780, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25898] Another function of VGAM615 is therefore inhibition of Farnesyltransferase, CAAX Box, Beta (FNTB, Accession NM\_002028), a gene which transfers farnesyl groups to proteins. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FNTB. The function of FNTB has been established by previous studies. Andres et al. (1993) localized the gene for the beta subunit of CAAX farnesyltransferase (FNTB) to 14q23–q24 by Southern blot hybridization and PCR analyses of panels of human/Chinese hamster somatic cell hybrid lines and by fluorescence chromosomal in situ hybridization. They found a related farnesyltransferase gene, FNTBL1, on chromosome 9. Long et al. (2002) presented a complete series of structures representing the major steps along the reaction coordinate of the enzyme protein farnesyltransferase. From

these observations, Long et al. (2002) deduced the determinants of substrate specificity and an unusual mechanism in which product release requires binding of substrate, analogous to classically processive enzymes. A structural model for the transition state consistent with previous mechanistic studies was also constructed.

[25899] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25900] Andres, D. A.; Milatovich, A.; Ozcelik, T.; Wenzlau, J. M.; Brown, M. S.; Goldstein, J. L.; Francke, U. : cDNA cloning of the two subunits of human CAAX farnesyltransferase and chromosomal mapping of FNTA and FNTB loci and related sequences. *Genomics* 18: 105–112, 1993. ; and

[25901] Long, S. B.; Casey, P. J.; Beese, L. S. : Reaction path of protein farnesyltransferase at atomic resolution. *Nature* 419: 645–650, 2002.

[25902] Further studies establishing the function and utilities of FNTB are found in John Hopkins OMIM database record ID 134636, and in cited publications numbered 11671–11672 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Forkhead Box D1 (FOXD1, Accession NM\_004472) is

another VGAM615 host target gene. FOXD1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FOXD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOXD1 BINDING SITE, designated SEQ ID:10778, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25903] Another function of VGAM615 is therefore inhibition of Forkhead Box D1 (FOXD1, Accession NM\_004472), a gene which has regulatory role in embryonic development. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOXD1. The function of FOXD1 has been established by previous studies. The forkhead genes are transcription factors distinguished by a characteristic 100-amino acid motif that was originally identified in *Drosophila* (see OMIM Ref. No. 164874). Pierrou et al. (1994) identified 7 human genes containing a forkhead domain and designated them forkhead related activators (FREAC) 1 through 7. Northern blot analysis revealed that the FREAC4, or FKHL8, gene is expressed as a 2.1-kb

mRNA exclusively in testis and kidney. These authors determined the DNA binding specificity of FKHL8 through selection of high affinity binding sites from random sequence oligonucleotides. Ernstsson et al. (1996) identified the human forkhead gene FREAC4 (FKHL8) as a nearly full-length cDNA and a 5.2-kb genomic fragment. The intronless gene predicts a protein of 465 amino acids with a hyperacidic N-terminal end, a DNA-binding forkhead domain, and a proline- and alanine-rich C-terminal end. The putative promoter region was active as a reporter fusion in the kidney-derived cell lines 293 and COS-7. Cotransfections with plasmids expressing WT1 (OMIM Ref. No. 607102), WTAR (a mutated form of WT1), p53 (OMIM Ref. No. 191170), and a mutated form of p53 revealed a complex pattern of regulation, suggesting that FREAC4 may be regulated by these gene products. Larsson et al. (1995) mapped the FKHL8 gene to 5q12-q13 by fluorescence in situ hybridization and somatic cell hybrid analysis.

[25904] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[25905] Ernstsson, S.; Pierrou, S.; Hulander, M.; Cederberg, A.; Hellqvist, M.; Carlsson, P.; Enerback, S. : Characterization

of the human forkhead gene FREAC-4. J. Biol. Chem. 271: 21094-21099, 1996. ; and

[25906] Larsson, C.; Hellqvist, M.; Pierrou, S.; White, I.; Enerback, S.; Carlsson, P. : Chromosomal localization of six human forkhead genes, freac-1 (FKHL5), -3 (FKHL7), -4 (FKHL8), -5 (FKHL9.

[25907] Further studies establishing the function and utilities of FOXD1 are found in John Hopkins OMIM database record ID 601091, and in cited publications numbered 9461-9460 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Potassium Intermediate/small Conductance Calcium-activated Channel, Subfamily N, Member 4 (KCNN4, Accession NM\_002250) is another VGAM615 host target gene. KCNN4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KCNN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNN4 BINDING SITE, designated SEQ ID:8035, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.



[25908] Another function of VGAM615 is therefore inhibition of Potassium Intermediate/small Conductance Calcium-activated Channel, Subfamily N, Member 4 (KCNN4, Accession NM\_002250), a gene which forms a voltage-independent potassium channel that is activated by intracellular calcium. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNN4. The function of KCNN4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152. Lymphocyte Antigen 6 Complex, Locus E (LY6E, Accession NM\_002346) is another VGAM615 host target gene. LY6E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LY6E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LY6E BINDING SITE, designated SEQ ID:8146, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25909] Another function of VGAM615 is therefore inhibition of Lymphocyte Antigen 6 Complex, Locus E (LY6E, Accession

NM\_002346). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LY6E. MAD, Mothers Against Decapentaplegic Homolog 4 (Drosophila) (MADH4, Accession NM\_005359) is another VGAM615 host target gene. MADH4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MADH4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MADH4 BINDING SITE, designated SEQ ID:11831, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25910] Another function of VGAM615 is therefore inhibition of MAD, Mothers Against Decapentaplegic Homolog 4 (Drosophila) (MADH4, Accession NM\_005359), a gene which common mediator of signal transduction by  $\text{tgf-}\beta$  (transforming growth factor) superfamily;  $\text{smad4}$  is the common  $\text{smad}$  (co- $\text{smad}$ ). promotes binding of the  $\text{smad2/smاد4/fast-1}$  complex to dna and provides an activation function required for  $\text{smad1}$  or  $\text{smad2}$  to stimulate transcription. may act as a tumor suppressor. Accord-

ingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MADH4. The function of MADH4 and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to

VGAM217. Microtubule-associated Protein Tau (MAPT, Accession NM\_016834) is another VGAM615 host target gene. MAPT BINDING SITE1 through MAPT BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MAPT, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPT BINDING SITE1 through MAPT BINDING SITE4, designated SEQ ID:18828, SEQ ID:12540, SEQ ID:18834 and SEQ ID:18840 respectively, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25911] Another function of VGAM615 is therefore inhibition of Microtubule-associated Protein Tau (MAPT, Accession NM\_016834), a gene which Microtubule-associated protein tau; promotes microtubule assembly. Accordingly,

utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPT. The function of MAPT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178. MLL Septin-like Fusion (MSF, Accession XM\_113892) is another VGAM615 host target gene. MSF BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MSF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSF BINDING SITE, designated SEQ ID:42523, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25912] Another function of VGAM615 is therefore inhibition of MLL Septin-like Fusion (MSF, Accession XM\_113892), a gene which plays a role in the cell cycle. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSF. The function of MSF and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference

to VGAM514. Neuroglobin (NGB, Accession NM\_021257) is another VGAM615 host target gene. NGB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NGB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NGB BINDING SITE, designated SEQ ID:22233, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25913] Another function of VGAM615 is therefore inhibition of Neuroglobin (NGB, Accession NM\_021257), a gene which has function in oxygen transport and storage in humans. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NGB. The function of NGB has been established by previous studies. By EST database searching for globin-like sequences, Burmester et al. (2000) identified cDNAs encoding human and mouse neuroglobin, symbolized NGB. Sequence analysis predicted that the 151-amino acid mouse and human proteins share 94% identity with each other but less than 25% identity with other vertebrate globins. RNA dot blot analysis revealed

predominant expression in the brain, with strongest signals observed in the frontal lobe, the subthalamic nucleus, and the thalamus. In situ hybridization analysis demonstrated expression in mouse brain neuronal cells. RT-PCR detected only trace amounts of Ngb in other mouse tissues. Biochemical purification and size-exclusion chromatographic analysis showed that Ngb is a 16-kD monomer, found in low concentrations in mouse brain, that reversibly binds oxygen with an affinity nearly as high as that of MB but higher than that of HB. Genomic sequence analysis of a PAC clone determined that the NGB gene has a 4 exon/3 intron structure, distinct from that of other globin genes, and a promoter region that contains several putative SP1 (OMIM Ref. No. 189906)-binding sites. Five-prime RACE identified at least 3 transcription starting points but no TATA box, suggesting a house-keeping promoter. In an accompanying editorial, Moens and Dewilde (2000) noted that regions of the brain with lower expression of NGB (e.g., hippocampus) have lower resistance to ischemia and are frequently affected by neurofibrillary tangles in Alzheimer disease.

[25914] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [25915] Burmester, T.; Weich, B.; Reinhardt, S.; Hankeln, T. : A vertebrate globin expressed in the brain. *Nature* 407: 520–523, 2000. ; and
- [25916] Moens, L.; Dewilde, S. : Globins in the brain. *Nature* 407: 461–462, 2000.
- [25917] Further studies establishing the function and utilities of NGB are found in John Hopkins OMIM database record ID 605304, and in cited publications numbered 7476–7477 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neuropeptide Y Receptor Y2 (NPY2R, Accession NM\_000910) is another VGAM615 host target gene. NPY2R BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NPY2R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NPY2R BINDING SITE, designated SEQ ID:6609, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.
- [25918] Another function of VGAM615 is therefore inhibition of Neuropeptide Y Receptor Y2 (NPY2R, Accession

NM\_000910), a gene which stimulates intracellular calcium flux and may modulate psychomotor activity, food intake, endocrine secretion and vasoconstriction. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NPY2R. The function of NPY2R and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM309. Pleckstrin Homology, Sec7 and Coiled/coil Domains 4 (PSCD4, Accession NM\_013385) is another VGAM615 host target gene. PSCD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSCD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSCD4 BINDING SITE, designated SEQ ID:15037, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25919] Another function of VGAM615 is therefore inhibition of Pleckstrin Homology, Sec7 and Coiled/coil Domains 4 (PSCD4, Accession NM\_013385), a gene which promotes



guanine–nucleotide exchange on arf1 and arf5. Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSCD4. The function of PSCD4 has been established by previous studies. ADP–ribosylation factors, or ARFS (see OMIM Ref. No. ARF1; 103180), are small GTP–binding proteins within the Ras superfamily that regulate vesicle trafficking in eukaryotic cells. ARF1 recruits coat proteins (e.g., COPA; 601924) to membranes on the cytoplasmic face of the Golgi apparatus. The PSCD proteins (e.g., PSCD1; 182115), a family of proteins containing a C–terminal pleckstrin homology (PH) domain and a central 200–amino acid region similar to a domain within the yeast Sec7 protein, which is required for vesicular traffic of polypeptides through the Golgi, function as guanine–nucleotide exchange factors (GEFs) for ARFs. Klarlund et al. (1997) identified a cDNA encoding mouse Grp1 (general receptor for phosphoinositides–1) by screening mouse adipocyte and brain cDNA expression libraries with phosphoinositide probes. By searching an EST database for sequences similar to mouse brain Grp1, followed by PCR and screening of a human blood cDNA library, Venkateswarlu et al. (1998) obtained a cDNA encoding

PSCD3, which they called GRP1. Sequence analysis showed that the predicted 399–amino acid PSCD3 protein contains a 39–amino acid coiled–coil domain, a 172–amino acid Sec7 domain, and a 118–amino acid PH domain. PSCD3 shares 82.7% and 79.5% amino acid identity with PSCD1 and PSCD2 (OMIM Ref. No. 602488), respectively, as well as 98.8% identity with mouse Grp1. By Scatchard and mutational analyses, Venkateswarlu et al. (1998) determined that PSCD3 binds via its PH domain to the inositol head group of phosphatidylinositol 3,4,5–triphosphate with high affinity. Confocal laser microscopy demonstrated that stimulation of cells with either epidermal growth factor (EGF; 131530) or nerve growth factor (NGF; 162030) results in PH domain–dependent translocation of PSCD3 from the cytosol to the plasma membrane. The translocation was rapid and transient with EGF, whereas NGF mediated a relatively longer translocation. By searching an EST database for Sec7 domain–related sequences and by screening a placenta cDNA library, Franco et al. (1998) isolated a cDNA encoding PSCD3, which they called ARNO3. Northern blot analysis revealed that PSCD3, in contrast to the ubiquitously expressed PSCD1 and PSCD2, is expressed as a 4.5–kb transcript that is almost absent

from liver, thymus, and peripheral blood lymphocytes. Franco et al. (1998) found that PSCD3, like PSCD1 and PSCD2, shows GEF activity, mediated by the Sec7 domain, towards ARF1 but not ARF6 (OMIM Ref. No. 600464). Immunofluorescence microscopy indicated that overexpression of PSCD3 induces major morphologic alterations of the Golgi apparatus, including redistribution of Golgi resident proteins and the coat protein COPB (OMIM Ref. No. 600959). Lietzke et al. (2000) and Ferguson et al. (2000) determined the structure of the GRP1 PH domain in the unliganded form and bound to inositol 1,3,4,5-tetraphosphate. Lietzke et al. (2000) found that a novel mode of phosphoinositide recognition involving a 20-residue insertion within the beta-6/beta-7 loop explains the unusually high specificity of the GRP1 PH domain and the promiscuous 3-phosphoinositide binding typical of several other PH domains, including that of protein kinase B (AKT1; 164730). By comparing the GRP1 PH domain to other PH domains, general determinants of 3-phosphoinositide recognition and specificity could be deduced.

[25920] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [25921] Ferguson, K. M.; Kavran, J. M.; Sankaran, V. G.; Fournier, E.; Isakoff, S. J.; Skolnik, E. Y.; Lemmon, M. A. : Structural basis for discrimination of 3-phosphoinositides by pleckstrin homology domains. *Molec. Cell* 6: 373–384, 2000. ; and
- [25922] Franco, M.; Boretto, J.; Robineau, S.; Monier, S.; Goud, B.; Chardin, P.; Chavrier, P. : ARNO3, a Sec7-domain guanine nucleotide exchange factor for ADP ribosylation factor 1, is invol.
- [25923] Further studies establishing the function and utilities of PSCD4 are found in John Hopkins OMIM database record ID 606514, and in cited publications numbered 10705 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RAN Binding Protein 3 (RANBP3, Accession NM\_003624) is another VGAM615 host target gene. RANBP3 BINDING SITE1 and RANBP3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RANBP3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RANBP3 BINDING SITE1 and RANBP3 BINDING SITE2, des-

ignated SEQ ID:9688 and SEQ ID:14240 respectively, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25924] Another function of VGAM615 is therefore inhibition of RAN Binding Protein 3 (RANBP3, Accession NM\_003624). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RANBP3. Chromosome 1 Open Reading Frame 2 (C1orf2, Accession NM\_006589) is another VGAM615 host target gene. C1orf2 BINDING SITE1 and C1orf2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by C1orf2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1orf2 BINDING SITE1 and C1orf2 BINDING SITE2, designated SEQ ID:13356 and SEQ ID:45396 respectively, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25925] Another function of VGAM615 is therefore inhibition of Chromosome 1 Open Reading Frame 2 (C1orf2, Accession NM\_006589). Accordingly, utilities of VGAM615 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf2. DKFZP434J193 (Accession XM\_048452) is another VGAM615 host target gene. DKFZP434J193 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434J193, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434J193 BINDING SITE, designated SEQ ID:35164, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25926] Another function of VGAM615 is therefore inhibition of DKFZP434J193 (Accession XM\_048452). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434J193. DKFZp586I021 (Accession NM\_032271) is another VGAM615 host target gene. DKFZp586I021 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp586I021, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of DKFZp586I021 BINDING SITE, designated SEQ ID:26021, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25927] Another function of VGAM615 is therefore inhibition of DKFZp586I021 (Accession NM\_032271). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp586I021. FLJ22215 (Accession NM\_022834) is another VGAM615 host target gene. FLJ22215 BINDING SITE1 and FLJ22215 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ22215, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22215 BINDING SITE1 and FLJ22215 BINDING SITE2, designated SEQ ID:23118 and SEQ ID:46280 respectively, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25928] Another function of VGAM615 is therefore inhibition of FLJ22215 (Accession NM\_022834). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ22215. KIAA0455 (Accession XM\_051785) is another VGAM615 host target gene. KIAA0455 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0455, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0455 BINDING SITE, designated SEQ ID:35881, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25929] Another function of VGAM615 is therefore inhibition of KIAA0455 (Accession XM\_051785). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0455. MCFP (Accession NM\_018843) is another VGAM615 host target gene. MCFP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MCFP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MCFP BINDING SITE, designated SEQ ID:20828, to the nucleotide sequence of



VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25930] Another function of VGAM615 is therefore inhibition of MCFP (Accession NM\_018843). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MCFP. MGC15730 (Accession NM\_032880) is another VGAM615 host target gene. MGC15730 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC15730, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15730 BINDING SITE, designated SEQ ID:26701, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25931] Another function of VGAM615 is therefore inhibition of MGC15730 (Accession NM\_032880). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15730. Neural Precursor Cell Expressed, Developmentally Down-regulated 5 (NEDD5, Accession NM\_004404) is another VGAM615 host target gene.

NEDD5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by NEDD5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEDD5 BINDING SITE, designated SEQ ID:10657, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25932] Another function of VGAM615 is therefore inhibition of Neural Precursor Cell Expressed, Developmentally Down-regulated 5 (NEDD5, Accession NM\_004404). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEDD5. LOC128710 (Accession XM\_059267) is another VGAM615 host target gene. LOC128710 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC128710, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC128710 BINDING SITE, designated SEQ ID:36934, to the nucleotide sequence of VGAM615 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3326.

[25933] Another function of VGAM615 is therefore inhibition of LOC128710 (Accession XM\_059267). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC128710. LOC146381 (Accession XM\_085439) is another VGAM615 host target gene. LOC146381 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146381, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146381 BINDING SITE, designated SEQ ID:38145, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25934] Another function of VGAM615 is therefore inhibition of LOC146381 (Accession XM\_085439). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146381. LOC197439 (Accession XM\_113889) is another VGAM615 host target gene. LOC197439 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC197439, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197439 BINDING SITE, designated SEQ ID:42517, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25935] Another function of VGAM615 is therefore inhibition of LOC197439 (Accession XM\_113889). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197439. LOC245811 (Accession XM\_168197) is another VGAM615 host target gene. LOC245811 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC245811, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC245811 BINDING SITE, designated SEQ ID:45070, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25936] Another function of VGAM615 is therefore inhibition of LOC245811 (Accession XM\_168197). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC245811. LOC92573 (Accession XM\_045884) is another VGAM615 host target gene. LOC92573 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92573, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92573 BINDING SITE, designated SEQ ID:34595, to the nucleotide sequence of VGAM615 RNA, herein designated VGAM RNA, also designated SEQ ID:3326.

[25937] Another function of VGAM615 is therefore inhibition of LOC92573 (Accession XM\_045884). Accordingly, utilities of VGAM615 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92573. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 616 (VGAM616) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25938] VGAM616 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM616 was detected is described hereinabove with reference to Figs. 1–8.

[25939] VGAM616 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Xestia C-nigrum Granulovirus. VGAM616 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25940] VGAM616 gene encodes a VGAM616 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM616 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM616 precursor RNA is designated SEQ ID:602, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:602 is located at position 128882 relative to the genome of Xestia C-nigrum Granulovirus.

[25941] VGAM616 precursor RNA folds onto itself, forming VGAM616 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25942] An enzyme complex designated DICER COMPLEX, `dices` the VGAM616 folded precursor RNA into VGAM616 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM616 RNA is designated SEQ ID:3327, and is provided hereinbelow with reference to the sequence listing part.

[25943] VGAM616 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM616 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM616 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25944] VGAM616 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM616 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM616 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM616 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM616 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25945] The complementary binding of VGAM616 RNA, herein



designated VGAM RNA, to host target binding sites on VGAM616 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM616 host target RNA into VGAM616 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25946] It is appreciated that VGAM616 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM616 host target genes. The mRNA of each one of this plurality of VGAM616 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM616 RNA, herein designated VGAM RNA, and which when bound by VGAM616 RNA causes inhibition of translation of respective one or more VGAM616 host target proteins.

[25947] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM616 gene, herein designated VGAM GENE, on one or more VGAM616 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25948] It is yet further appreciated that a function of VGAM616 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of viral infection by Xestia C-nigrum Granulovirus. Specific functions, and accordingly utilities, of VGAM616 correlate with, and may be deduced from, the identity of the host target genes which VGAM616 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25949] Nucleotide sequences of the VGAM616 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM616 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM616 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM616 are further described hereinbelow with reference to Table 1.

[25950] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM616 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM616 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25951] As mentioned hereinabove with reference to Fig. 1, a function of VGAM616 gene, herein designated VGAM is inhibition of expression of VGAM616 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM616 correlate with, and may be deduced from, the identity of the target genes which VGAM616 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25952] Copine III (CPNE3, Accession NM\_003909) is a VGAM616 host target gene. CPNE3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA

encoded by CPNE3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CPNE3 BINDING SITE, designated SEQ ID:9998, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25953] A function of VGAM616 is therefore inhibition of Copine III (CPNE3, Accession NM\_003909), a gene which may function in membrane trafficking. Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CPNE3. The function of CPNE3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM28. Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005) is another VGAM616 host target gene. PCDHA9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA9 BINDING SITE, designated SEQ

ID:15216, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25954] Another function of VGAM616 is therefore inhibition of Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005), a gene which is a calcium-dependent cell-adhesion protein. Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA9. The function of PCDHA9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM71.Src-like-adaptor (SLA, Accession NM\_006748) is another VGAM616 host target gene. SLA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLA BINDING SITE, designated SEQ ID:13595, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25955] Another function of VGAM616 is therefore inhibition of

Src-like-adaptor (SLA, Accession NM\_006748), a gene which is a negative regulator of T-cell receptor signaling. Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLA. The function of SLA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM383. ARHGAP10 (Accession NM\_020824) is another VGAM616 host target gene. ARHGAP10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGAP10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP10 BINDING SITE, designated SEQ ID:21889, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25956] Another function of VGAM616 is therefore inhibition of ARHGAP10 (Accession NM\_020824). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP10. BCL2-associated Athanogene 5 (BAG5, Acces-

sion NM\_004873) is another VGAM616 host target gene. BAG5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BAG5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BAG5 BINDING SITE, designated SEQ ID:11308, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25957] Another function of VGAM616 is therefore inhibition of BCL2-associated Athanogene 5 (BAG5, Accession NM\_004873). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BAG5. Chromosome 20 Open Reading Frame 45 (C20orf45, Accession NM\_016045) is another VGAM616 host target gene. C20orf45 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf45, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf45 BINDING SITE, designated SEQ ID:18123, to the nucleotide sequence of VGAM616 RNA,

herein designated VGAM RNA, also designated SEQ ID:3327.

[25958] Another function of VGAM616 is therefore inhibition of Chromosome 20 Open Reading Frame 45 (C20orf45, Accession NM\_016045). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf45.

FLJ14437 (Accession NM\_032578) is another VGAM616 host target gene. FLJ14437 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14437, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14437 BINDING SITE, designated SEQ ID:26311, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25959] Another function of VGAM616 is therefore inhibition of FLJ14437 (Accession NM\_032578). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14437. FLJ20725 (Accession NM\_017943) is another VGAM616 host target gene. FLJ20725 BINDING SITE is HOST TARGET



binding site found in the 3' untranslated region of mRNA encoded by FLJ20725, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20725 BINDING SITE, designated SEQ ID:19637, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25960] Another function of VGAM616 is therefore inhibition of FLJ20725 (Accession NM\_017943). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20725. KIAA0350 (Accession XM\_028332) is another VGAM616 host target gene. KIAA0350 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0350 BINDING SITE, designated SEQ ID:30667, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25961] Another function of VGAM616 is therefore inhibition of

KIAA0350 (Accession XM\_028332). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0350. KIAA0947 (Accession XM\_029101) is another VGAM616 host target gene. KIAA0947 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0947, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0947 BINDING SITE, designated SEQ ID:30849, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25962] Another function of VGAM616 is therefore inhibition of KIAA0947 (Accession XM\_029101). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0947. KIAA1322 (Accession XM\_052626) is another VGAM616 host target gene. KIAA1322 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1322 BINDING SITE, designated SEQ ID:36026, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25963] Another function of VGAM616 is therefore inhibition of KIAA1322 (Accession XM\_052626). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1322. KIAA1376 (Accession XM\_033042) is another VGAM616 host target gene. KIAA1376 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1376, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1376 BINDING SITE, designated SEQ ID:31824, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25964] Another function of VGAM616 is therefore inhibition of KIAA1376 (Accession XM\_033042). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1376. KIAA1870 (Accession NM\_032161) is another

VGAM616 host target gene. KIAA1870 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1870, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1870 BINDING SITE, designated SEQ ID:25862, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25965] Another function of VGAM616 is therefore inhibition of KIAA1870 (Accession NM\_032161). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1870. MBLL39 (Accession NM\_144778) is another VGAM616 host target gene. MBLL39 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MBLL39, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MBLL39 BINDING SITE, designated SEQ ID:29569, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25966] Another function of VGAM616 is therefore inhibition of MBLL39 (Accession NM\_144778). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBLL39. SCYB10 (Accession NM\_001565) is another VGAM616 host target gene. SCYB10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCYB10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCYB10 BINDING SITE, designated SEQ ID:7294, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25967] Another function of VGAM616 is therefore inhibition of SCYB10 (Accession NM\_001565). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCYB10. LOC151877 (Accession XM\_098132) is another VGAM616 host target gene. LOC151877 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151877, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151877 BINDING SITE, designated SEQ ID:41396, to the nucleotide sequence of VGAM616 RNA, herein designated VGAM RNA, also designated SEQ ID:3327.

[25968] Another function of VGAM616 is therefore inhibition of LOC151877 (Accession XM\_098132). Accordingly, utilities of VGAM616 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151877. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 617 (VGAM617) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25969] VGAM617 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM617 was detected is described hereinabove with reference to Figs. 1–8.

[25970] VGAM617 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Xestia C-nigrum Granulovirus. VGAM617 host target gene, herein designated

VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25971] VGAM617 gene encodes a VGAM617 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM617 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM617 precursor RNA is designated SEQ ID:603, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:603 is located at position 140057 relative to the genome of Xes-tia C-nigrum Granulovirus.

[25972] VGAM617 precursor RNA folds onto itself, forming VGAM617 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25973] An enzyme complex designated DICER COMPLEX, `dices` the VGAM617 folded precursor RNA into VGAM617 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM617 RNA is designated SEQ ID:3328, and is provided hereinbelow with reference to the sequence listing part.

[25974] VGAM617 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM617 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM617 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25975] VGAM617 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM617 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM617 RNA is an accurate or a



partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM617 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM617 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25976] The complementary binding of VGAM617 RNA, herein designated VGAM RNA, to host target binding sites on VGAM617 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM617 host target RNA into VGAM617 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[25977] It is appreciated that VGAM617 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM617 host target genes. The mRNA of each one of this plurality of VGAM617 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM617 RNA, herein designated VGAM RNA, and which when bound by VGAM617 RNA causes inhibition of translation of respective one or more VGAM617 host target proteins.

[25978] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM617 gene, herein designated VGAM GENE, on one or more VGAM617 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25979] It is yet further appreciated that a function of VGAM617 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM617 include diagnosis, prevention and treatment of viral infection by Xestia C-nigrum Granulovirus. Specific functions, and accordingly utilities, of VGAM617 correlate with, and may be deduced from, the identity of the host target genes which VGAM617 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25980] Nucleotide sequences of the VGAM617 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM617 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM617 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM617 are further described hereinbelow with reference to Table 1.

[25981] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM617 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM617 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[25982] As mentioned hereinabove with reference to Fig. 1, a function of VGAM617 gene, herein designated VGAM is inhibition of expression of VGAM617 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM617 correlate with, and may be deduced from, the identity of the target genes which VGAM617 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[25983] LOC154442 (Accession XM\_098536) is a VGAM617 host target gene. LOC154442 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154442, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154442 BINDING SITE, designated SEQ ID:41706, to the nucleotide sequence of VGAM617 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3328.

[25984] A function of VGAM617 is therefore inhibition of LOC154442 (Accession XM\_098536). Accordingly, utilities of VGAM617 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154442. LOC51279 (Accession NM\_016546) is another VGAM617 host target gene. LOC51279 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51279, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51279 BINDING SITE, designated SEQ ID:18613, to the nucleotide sequence of VGAM617 RNA, herein designated VGAM RNA, also designated SEQ ID:3328.

[25985] Another function of VGAM617 is therefore inhibition of LOC51279 (Accession NM\_016546). Accordingly, utilities of VGAM617 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51279. LOC51336 (Accession NM\_016646) is another VGAM617 host target gene. LOC51336 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51336, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51336 BINDING SITE, designated SEQ ID:18760, to the nucleotide sequence of VGAM617 RNA, herein designated VGAM RNA, also designated SEQ ID:3328.

[25986] Another function of VGAM617 is therefore inhibition of LOC51336 (Accession NM\_016646). Accordingly, utilities of VGAM617 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51336. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 618 (VGAM618) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[25987] VGAM618 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM618 was detected is described hereinabove with reference to Figs. 1–8.

[25988] VGAM618 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rabbit Oral Papillo–

mavirus. VGAM618 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[25989] VGAM618 gene encodes a VGAM618 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM618 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM618 precursor RNA is designated SEQ ID:604, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:604 is located at position 4111 relative to the genome of Rabbit Oral Papillomavirus.

[25990] VGAM618 precursor RNA folds onto itself, forming VGAM618 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[25991] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM618 folded precursor RNA into VGAM618 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM618 RNA is designated SEQ ID:3329, and is provided hereinbelow with reference to the sequence listing part.

[25992] VGAM618 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM618 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM618 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[25993] VGAM618 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM618 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-



cleotide sequence of VGAM618 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM618 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM618 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[25994] The complementary binding of VGAM618 RNA, herein designated VGAM RNA, to host target binding sites on VGAM618 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM618 host target RNA into VGAM618 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[25995] It is appreciated that VGAM618 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM618 host target genes. The mRNA of each one of this plurality of VGAM618 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM618 RNA, herein designated VGAM RNA, and which when bound by VGAM618 RNA causes inhibition of translation of respective one or more VGAM618 host target proteins.

[25996] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM618 gene, herein designated VGAM GENE, on one or more VGAM618 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[25997] It is yet further appreciated that a function of VGAM618 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM618 include diagnosis, prevention and treatment of viral infection by Rabbit Oral Papillomavirus. Specific functions, and accordingly utilities, of VGAM618 correlate with, and may be deduced from, the identity of the host target genes which VGAM618 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[25998] Nucleotide sequences of the VGAM618 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM618 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM618 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM618 are further described hereinbelow with reference to Table 1.

[25999] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM618 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM618 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26000] As mentioned hereinabove with reference to Fig. 1, a function of VGAM618 gene, herein designated VGAM is inhibition of expression of VGAM618 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM618 correlate with, and may be deduced from, the identity of the target genes which VGAM618 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26001] UDP-Gal:betaGlcNAc Beta 1,4- Galactosyltransferase, Polypeptide 4 (B4GALT4, Accession NM\_003778) is a VGAM618 host target gene. B4GALT4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by B4GALT4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B4GALT4

BINDING SITE, designated SEQ ID:9857, to the nucleotide sequence of VGAM618 RNA, herein designated VGAM RNA, also designated SEQ ID:3329.

[26002] A function of VGAM618 is therefore inhibition of UDP-Gal:betaGlcNAc Beta 1,4- Galactosyltransferase, Polypeptide 4 (B4GALT4, Accession NM\_003778). Accordingly, utilities of VGAM618 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B4GALT4. Macrophage Scavenger Receptor 1 (MSR1, Accession NM\_002445) is another VGAM618 host target gene. MSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSR1 BINDING SITE, designated SEQ ID:8284, to the nucleotide sequence of VGAM618 RNA, herein designated VGAM RNA, also designated SEQ ID:3329.

[26003] Another function of VGAM618 is therefore inhibition of Macrophage Scavenger Receptor 1 (MSR1, Accession NM\_002445), a gene which plays a role in endocytosis of macromolecules. Accordingly, utilities of VGAM618 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with MSR1. The function of MSR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM176. Solute Carrier Family 12, (potassium–chloride transporter) Member 5 (SLC12A5, Accession NM\_020708) is another VGAM618 host target gene. SLC12A5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC12A5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC12A5 BINDING SITE, designated SEQ ID:21854, to the nucleotide sequence of VGAM618 RNA, herein designated VGAM RNA, also designated SEQ ID:3329.

[26004] Another function of VGAM618 is therefore inhibition of Solute Carrier Family 12, (potassium–chloride transporter) Member 5 (SLC12A5, Accession NM\_020708). Accordingly, utilities of VGAM618 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC12A5. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic

Address Messenger 619 (VGAM619) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26005] VGAM619 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM619 was detected is described hereinabove with reference to Figs. 1–8.

[26006] VGAM619 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM619 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26007] VGAM619 gene encodes a VGAM619 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM619 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM619 precursor RNA is designated SEQ ID:605, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:605 is located at position 8778 relative to the genome of Hepatitis GB Virus C.

[26008] VGAM619 precursor RNA folds onto itself, forming VGAM619 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26009] An enzyme complex designated DICER COMPLEX, `dices` the VGAM619 folded precursor RNA into VGAM619 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM619 RNA is designated SEQ ID:3330, and is provided hereinbelow with reference to the sequence listing part.

[26010] VGAM619 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM619 host target RNA, herein designated VGAM



HOST TARGET RNA. VGAM619 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26011] VGAM619 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM619 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM619 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM619 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM619 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26012] The complementary binding of VGAM619 RNA, herein designated VGAM RNA, to host target binding sites on VGAM619 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM619 host target RNA into VGAM619 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26013] It is appreciated that VGAM619 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM619 host target genes. The mRNA of each one of this plurality of VGAM619 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM619 RNA, herein designated VGAM RNA, and which when bound by VGAM619 RNA causes inhibition of translation of respective one or more VGAM619 host target proteins.

[26014] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM619 gene, herein designated VGAM GENE, on one or more VGAM619 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26015] It is yet further appreciated that a function of VGAM619 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM619 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM619 correlate with, and may be deduced from, the identity of the

host target genes which VGAM619 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26016] Nucleotide sequences of the VGAM619 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM619 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM619 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM619 are further described hereinbelow with reference to Table 1.

[26017] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM619 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM619 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26018] As mentioned hereinabove with reference to Fig. 1, a function of VGAM619 gene, herein designated VGAM is inhibition of expression of VGAM619 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM619 correlate with, and may be deduced from, the identity of the target genes which VGAM619

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26019] Solute Carrier Family 21 (organic anion transporter), Member 11 (SLC21A11, Accession XM\_035268) is a VGAM619 host target gene. SLC21A11 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SLC21A11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC21A11 BINDING SITE, designated SEQ ID:32207, to the nucleotide sequence of VGAM619 RNA, herein designated VGAM RNA, also designated SEQ ID:3330.

[26020] A function of VGAM619 is therefore inhibition of Solute Carrier Family 21 (organic anion transporter), Member 11 (SLC21A11, Accession XM\_035268). Accordingly, utilities of VGAM619 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC21A11. LOC151429 (Accession XM\_098059) is another VGAM619 host target gene. LOC151429 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC151429, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151429 BINDING SITE, designated SEQ ID:41341, to the nucleotide sequence of VGAM619 RNA, herein designated VGAM RNA, also designated SEQ ID:3330.

[26021] Another function of VGAM619 is therefore inhibition of LOC151429 (Accession XM\_098059). Accordingly, utilities of VGAM619 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151429. LOC153572 (Accession XM\_098392) is another VGAM619 host target gene. LOC153572 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC153572, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153572 BINDING SITE, designated SEQ ID:41639, to the nucleotide sequence of VGAM619 RNA, herein designated VGAM RNA, also designated SEQ ID:3330.

[26022] Another function of VGAM619 is therefore inhibition of LOC153572 (Accession XM\_098392). Accordingly, utilities of VGAM619 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC153572. LOC155340 (Accession XM\_055725) is another VGAM619 host target gene. LOC155340 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC155340, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155340 BINDING SITE, designated SEQ ID:36318, to the nucleotide sequence of VGAM619 RNA, herein designated VGAM RNA, also designated SEQ ID:3330.

[26023] Another function of VGAM619 is therefore inhibition of LOC155340 (Accession XM\_055725). Accordingly, utilities of VGAM619 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155340. LOC93052 (Accession XM\_048905) is another VGAM619 host target gene. LOC93052 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC93052, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93052 BINDING SITE, designated SEQ ID:35302, to the nucleotide sequence of VGAM619 RNA, herein designated

VGAM RNA, also designated SEQ ID:3330.

[26024] Another function of VGAM619 is therefore inhibition of LOC93052 (Accession XM\_048905). Accordingly, utilities of VGAM619 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93052. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 620 (VGAM620) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26025] VGAM620 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM620 was detected is described hereinabove with reference to Figs. 1–8.

[26026] VGAM620 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM620 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26027] VGAM620 gene encodes a VGAM620 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other



miRNA genes, and unlike most ordinary genes, VGAM620 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM620 precursor RNA is designated SEQ ID:606, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:606 is located at position 3307 relative to the genome of Hepatitis GB Virus C.

[26028] VGAM620 precursor RNA folds onto itself, forming VGAM620 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26029] An enzyme complex designated DICER COMPLEX, `dices` the VGAM620 folded precursor RNA into VGAM620 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM620 RNA is designated SEQ ID:3331, and is provided hereinbelow with reference to the sequence listing part.

[26030] VGAM620 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM620 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM620 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[26031] VGAM620 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM620 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM620 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM620 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM620 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[26032] The complementary binding of VGAM620 RNA, herein designated VGAM RNA, to host target binding sites on VGAM620 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM620 host target RNA into VGAM620 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26033] It is appreciated that VGAM620 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM620 host target genes. The mRNA of

each one of this plurality of VGAM620 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM620 RNA, herein designated VGAM RNA, and which when bound by VGAM620 RNA causes inhibition of translation of respective one or more VGAM620 host target proteins.

[26034] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM620 gene, herein designated VGAM GENE, on one or more VGAM620 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[26035] It is yet further appreciated that a function of VGAM620 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM620 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM620 correlate with, and may be deduced from, the identity of the host target genes which VGAM620 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26036] Nucleotide sequences of the VGAM620 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM620 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM620 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM620 are further described hereinbelow with reference to Table 1.

[26037] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM620 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM620 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[26038] As mentioned hereinabove with reference to Fig. 1, a function of VGAM620 gene, herein designated VGAM is inhibition of expression of VGAM620 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM620 correlate with, and may be deduced from, the identity of the target genes which VGAM620 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26039] FLJ10781 (Accession NM\_018215) is a VGAM620 host target gene. FLJ10781 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10781, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10781 BINDING SITE, designated SEQ ID:20136, to the nucleotide sequence of VGAM620 RNA, herein designated VGAM RNA, also designated SEQ ID:3331.

[26040] A function of VGAM620 is therefore inhibition of FLJ10781 (Accession NM\_018215). Accordingly, utilities of VGAM620 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ10781. KIAA0182 (Accession XM\_050495) is another VGAM620 host target gene. KIAA0182 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0182, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0182 BINDING SITE, designated SEQ ID:35647, to the nucleotide sequence of VGAM620 RNA, herein designated VGAM RNA, also designated SEQ ID:3331.

[26041] Another function of VGAM620 is therefore inhibition of KIAA0182 (Accession XM\_050495). Accordingly, utilities of VGAM620 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0182. LOC151610 (Accession XM\_087245) is another VGAM620 host target gene. LOC151610 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151610, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151610 BINDING SITE, designated SEQ ID:39135, to

the nucleotide sequence of VGAM620 RNA, herein designated VGAM RNA, also designated SEQ ID:3331.

[26042] Another function of VGAM620 is therefore inhibition of LOC151610 (Accession XM\_087245). Accordingly, utilities of VGAM620 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151610. LOC157958 (Accession XM\_088431) is another VGAM620 host target gene. LOC157958 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157958, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157958 BINDING SITE, designated SEQ ID:39685, to the nucleotide sequence of VGAM620 RNA, herein designated VGAM RNA, also designated SEQ ID:3331.

[26043] Another function of VGAM620 is therefore inhibition of LOC157958 (Accession XM\_088431). Accordingly, utilities of VGAM620 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157958. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-



dress Messenger 621 (VGAM621) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26044] VGAM621 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM621 was detected is described hereinabove with reference to Figs. 1–8.

[26045] VGAM621 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM621 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26046] VGAM621 gene encodes a VGAM621 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM621 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM621 precursor RNA is designated SEQ ID:607, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:607 is located at position 757 relative to the genome of Hepatitis GB Virus C.

[26047] VGAM621 precursor RNA folds onto itself, forming VGAM621 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26048] An enzyme complex designated DICER COMPLEX, `dices` the VGAM621 folded precursor RNA into VGAM621 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM621 RNA is designated SEQ ID:3332, and is provided hereinbelow with reference to the sequence listing part.

[26049] VGAM621 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM621 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM621 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26050] VGAM621 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM621 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM621 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM621 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM621 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26051] The complementary binding of VGAM621 RNA, herein designated VGAM RNA, to host target binding sites on VGAM621 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM621 host target RNA into VGAM621 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26052] It is appreciated that VGAM621 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM621 host target genes. The mRNA of each one of this plurality of VGAM621 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM621 RNA, herein designated VGAM RNA, and which when bound by VGAM621 RNA causes inhibition of translation of respective one or more VGAM621 host target proteins.

[26053] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM621 gene, herein designated VGAM GENE, on one or more VGAM621 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26054] It is yet further appreciated that a function of VGAM621 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM621 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM621 correlate with, and may be deduced from, the identity of the

host target genes which VGAM621 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26055] Nucleotide sequences of the VGAM621 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM621 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM621 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM621 are further described hereinbelow with reference to Table 1.

[26056] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM621 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM621 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26057] As mentioned hereinabove with reference to Fig. 1, a function of VGAM621 gene, herein designated VGAM is inhibition of expression of VGAM621 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM621 correlate with, and may be deduced from, the identity of the target genes which VGAM621

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26058] poly(A) Binding Protein, Cytoplasmic 1 (PABPC1, Accession NM\_002568) is a VGAM621 host target gene. PABPC1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PABPC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PABPC1 BINDING SITE, designated SEQ ID:8418, to the nucleotide sequence of VGAM621 RNA, herein designated VGAM RNA, also designated SEQ ID:3332.

[26059] A function of VGAM621 is therefore inhibition of poly(A) Binding Protein, Cytoplasmic 1 (PABPC1, Accession NM\_002568), a gene which involves in cytoplasmic regulatory processes of mRNA metabolism. Accordingly, utilities of VGAM621 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PABPC1. The function of PABPC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM280. Polymerase (DNA directed) Sigma (POLS, Accession NM\_006999) is another VGAM621 host

target gene. POLS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POLS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POLS BINDING SITE, designated SEQ ID:13864, to the nucleotide sequence of VGAM621 RNA, herein designated VGAM RNA, also designated SEQ ID:3332.

[26060] Another function of VGAM621 is therefore inhibition of Polymerase (DNA directed) Sigma (POLS, Accession NM\_006999), a gene which is necessary for chromosome segregation. Accordingly, utilities of VGAM621 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POLS. The function of POLS and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM106.CD36L2 (Accession NM\_005506) is another VGAM621 host target gene. CD36L2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CD36L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.



Table 2 illustrates the complementarity of the nucleotide sequences of CD36L2 BINDING SITE, designated SEQ ID:12021, to the nucleotide sequence of VGAM621 RNA, herein designated VGAM RNA, also designated SEQ ID:3332.

[26061] Another function of VGAM621 is therefore inhibition of CD36L2 (Accession NM\_005506). Accordingly, utilities of VGAM621 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD36L2. Protein-O-mannosyltransferase 1 (POMT1, Accession NM\_007171) is another VGAM621 host target gene. POMT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POMT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of POMT1 BINDING SITE, designated SEQ ID:14015, to the nucleotide sequence of VGAM621 RNA, herein designated VGAM RNA, also designated SEQ ID:3332.

[26062] Another function of VGAM621 is therefore inhibition of Protein-O-mannosyltransferase 1 (POMT1, Accession NM\_007171). Accordingly, utilities of VGAM621 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with POMT1. Rab11-FIP3 (Accession NM\_014700) is another VGAM621 host target gene. Rab11-FIP3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by Rab11-FIP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Rab11-FIP3 BINDING SITE, designated SEQ ID:16225, to the nucleotide sequence of VGAM621 RNA, herein designated VGAM RNA, also designated SEQ ID:3332.

[26063] Another function of VGAM621 is therefore inhibition of Rab11-FIP3 (Accession NM\_014700). Accordingly, utilities of VGAM621 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rab11-FIP3. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 622 (VGAM622) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26064] VGAM622 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM622 was detected is described hereinabove with reference to Figs. 1–8.

[26065] VGAM622 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM622 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26066] VGAM622 gene encodes a VGAM622 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM622 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM622 precursor RNA is designated SEQ ID:608, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:608 is located at position 6041 relative to the genome of Hepatitis GB Virus C.

[26067] VGAM622 precursor RNA folds onto itself, forming VGAM622 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26068] An enzyme complex designated DICER COMPLEX, `dices` the VGAM622 folded precursor RNA into VGAM622 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 55%) nucleotide sequence of VGAM622 RNA is designated SEQ ID:3333, and is provided hereinbelow with reference to the sequence listing part.

[26069] VGAM622 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM622 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM622 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[26070] VGAM622 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM622 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM622 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM622 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM622 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26071] The complementary binding of VGAM622 RNA, herein designated VGAM RNA, to host target binding sites on VGAM622 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM622 host target RNA into VGAM622 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26072] It is appreciated that VGAM622 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM622 host target genes. The mRNA of each one of this plurality of VGAM622 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM622 RNA, herein designated VGAM RNA, and which when bound by VGAM622 RNA causes inhibition of translation of respective one or more VGAM622 host target proteins.

[26073] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM622 gene, herein designated VGAM GENE, on one or more VGAM622 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26074] It is yet further appreciated that a function of VGAM622 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM622 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM622 correlate with, and may be deduced from, the identity of the host target genes which VGAM622 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26075] Nucleotide sequences of the VGAM622 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM622 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM622 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM622 are further  
described hereinbelow with reference to Table 1.

[26076] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM622 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM622 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[26077] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM622 gene, herein designated VGAM is  
inhibition of expression of VGAM622 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM622 correlate with, and may be deduced  
from, the identity of the target genes which VGAM622  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[26078] Potassium Voltage-gated Channel, KQT-like Subfamily,  
Member 1 (KCNQ1, Accession NM\_000218) is a VGAM622



host target gene. KCNQ1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNQ1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNQ1 BINDING SITE, designated SEQ ID:5722, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26079] A function of VGAM622 is therefore inhibition of Potassium Voltage-gated Channel, KQT-like Subfamily, Member 1 (KCNQ1, Accession NM\_000218), a gene which probably important in cardiac repolarization. associates with kcne1 (mink) to form the i(k<sub>s</sub>) cardiac potassium current. elicits a rapidly activating, k(+)-selective outward current. muscarinic agonist oxotremorine-m strongly suppresses kcnq1/kcne1 current in cho cells in which cloned kcnq1/kcne1 channels were coexpressed with m1 muscarinic receptors. may associate also with kcne3 (mirp2) to form the potassium channel that is important for cyclic amp-stimulated intestinal secretion of chloride  
io TISSUE:abondantly expressed in heart, pancreas, prostate, kidney, small intestine and peripheral blood

leukocytes. less abundant in placenta, lung, spleen, colon, thymus, testis and ovaries. Accordingly, utilities of VGAM622 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNQ1. The function of KCNQ1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM339. Regulatory Factor X, 2 (influences HLA class II expression) (RFX2, Accession NM\_000635) is another VGAM622 host target gene. RFX2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RFX2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RFX2 BINDING SITE, designated SEQ ID:6270, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26080] Another function of VGAM622 is therefore inhibition of Regulatory Factor X, 2 (influences HLA class II expression) (RFX2, Accession NM\_000635), a gene which acts as a dimer to regulate the expression of many genes. Accordingly, utilities of VGAM622 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with RFX2. The function of RFX2 has been established by previous studies. Pugliatti et al. (1992) noted that the expression of HLA class II genes (DR, DQ, and DP) is controlled primarily by cis-acting DNA motifs located within the 150 bp upstream of the genes and in particular by 2 highly conserved sequences, the X and Y boxes. Several protein factors bind to these cis-acting sequences. RFX is of special interest since a specific defect in its binding to target DNA sequence has been observed in patients with HLA class II deficient combined immunodeficiency (see OMIM Ref. No. 209920). Overexpression of RFX in transfected cells transactivates an HLA class II promoter, and antisense RNA expressed in transfected cells inhibits the expression of HLA-DR genes. A closely related form of RFX, referred to as RFX2, has also been isolated. The RFX1 (OMIM Ref. No. 600006) gene product is a transactivator of the human hepatitis B viral enhancer I. Reith et al. (1994) commented that the RFX family members, particularly RFX1 and RFX3 (OMIM Ref. No. 601337), constitute the nuclear complexes referred to previously as enhancer factor C (EF-C), EP, and methylation-dependent DNA-binding protein (MDBP), or rpL30-alpha. Reith et al.

(1994) identified and cloned 3 members of this gene family from both human and mouse using lambda gt11 cDNA libraries. The gene encoding human RFX2 encodes a 721-amino acid polypeptide. Homology between the 3 RFX proteins is restricted largely to 5 conserved regions, including the 2 domains required for DNA binding and dimerization. Reith et al. (1994) found that RFX1, RFX2, and RFX3 have similar DNA-binding specificities. The RFX monomers can heterodimerize both in vivo and in vitro, but all 3 are capable of binding DNA as monomers. They showed that the RFX2 transcript is particularly elevated in mouse testis.

[26081] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26082] Pugliatti, L.; Derre, J.; Berger, R.; Ucla, C.; Reith, W.; Mach, B. : The genes for MHC class II regulatory factors RFX1 and RFX2 are located on the short arm of chromosome 19. Genomics 13: 1307–1310, 1992. ; and

[26083] Reith, W.; Ucla, C.; Barras, E.; Gaud, A.; Durand, B.; Herrero-Sanchez, C.; Kobr, M.; Mach, B. : RFX1, a transactivator of hepatitis B virus enhancer I, belongs to a novel family of hom.

[26084] Further studies establishing the function and utilities of RFX2 are found in John Hopkins OMIM database record ID 142765, and in cited publications numbered 4745–4747 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FK506 Binding Protein 5 (FKBP5, Accession NM\_004117) is another VGAM622 host target gene. FKBP5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FKBP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FKBP5 BINDING SITE, designated SEQ ID:10323, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26085] Another function of VGAM622 is therefore inhibition of FK506 Binding Protein 5 (FKBP5, Accession NM\_004117). Accordingly, utilities of VGAM622 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FKBP5. MGC20576 (Accession NM\_144691) is another VGAM622 host target gene. MGC20576 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by

MGC20576, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC20576 BINDING SITE, designated SEQ ID:29510, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26086] Another function of VGAM622 is therefore inhibition of MGC20576 (Accession NM\_144691). Accordingly, utilities of VGAM622 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC20576. Oxysterol Binding Protein-like 5 (OSBPL5, Accession XM\_052567) is another VGAM622 host target gene. OSBPL5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OSBPL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSBPL5 BINDING SITE, designated SEQ ID:35987, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26087] Another function of VGAM622 is therefore inhibition of

Oxysterol Binding Protein-like 5 (OSBPL5, Accession XM\_052567). Accordingly, utilities of VGAM622 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OSBPL5. Purinergic Receptor P2X-like 1, Orphan Receptor (P2RXL1, Accession NM\_005446) is another VGAM622 host target gene. P2RXL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P2RXL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P2RXL1 BINDING SITE, designated SEQ ID:11927, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26088] Another function of VGAM622 is therefore inhibition of Purinergic Receptor P2X-like 1, Orphan Receptor (P2RXL1, Accession NM\_005446). Accordingly, utilities of VGAM622 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P2RXL1. RA-GEF-2 (Accession NM\_016340) is another VGAM622 host target gene. RA-GEF-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by RA-GEF-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RA-GEF-2 BINDING SITE, designated SEQ ID:18462, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26089] Another function of VGAM622 is therefore inhibition of RA-GEF-2 (Accession NM\_016340). Accordingly, utilities of VGAM622 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RA-GEF-2. LOC197358 (Accession XM\_113872) is another VGAM622 host target gene. LOC197358 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197358, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197358 BINDING SITE, designated SEQ ID:42507, to the nucleotide sequence of VGAM622 RNA, herein designated VGAM RNA, also designated SEQ ID:3333.

[26090] Another function of VGAM622 is therefore inhibition of LOC197358 (Accession XM\_113872). Accordingly, utilities



of VGAM622 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197358. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 623 (VGAM623) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26091] VGAM623 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM623 was detected is described hereinabove with reference to Figs. 1–8.

[26092] VGAM623 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM623 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26093] VGAM623 gene encodes a VGAM623 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM623 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM623 precursor RNA is designated SEQ ID:609, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:609 is located at position 1610 relative to the genome of Hepatitis GB Virus C.

[26094] VGAM623 precursor RNA folds onto itself, forming VGAM623 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26095] An enzyme complex designated DICER COMPLEX, `dices` the VGAM623 folded precursor RNA into VGAM623 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 54%) nucleotide sequence of VGAM623 RNA is designated SEQ ID:3334, and

is provided hereinbelow with reference to the sequence listing part.

[26096] VGAM623 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM623 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM623 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26097] VGAM623 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM623 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM623 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM623 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM623 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26098] The complementary binding of VGAM623 RNA, herein designated VGAM RNA, to host target binding sites on VGAM623 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM623 host target RNA into VGAM623 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26099] It is appreciated that VGAM623 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM623 host target genes. The mRNA of each one of this plurality of VGAM623 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM623 RNA, herein designated VGAM RNA, and which when bound by VGAM623 RNA causes inhibition of translation of respective one or more VGAM623 host target proteins.

[26100] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM623 gene, herein designated VGAM GENE, on one or more VGAM623 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26101] It is yet further appreciated that a function of VGAM623 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM623 correlate with, and may be deduced from, the identity of the host target genes which VGAM623 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26102] Nucleotide sequences of the VGAM623 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM623 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM623 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM623 are further described hereinbelow with reference to Table 1.

[26103] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM623 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM623 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26104] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM623 gene, herein designated VGAM is inhibition of expression of VGAM623 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM623 correlate with, and may be deduced from, the identity of the target genes which VGAM623 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26105] Chloride Channel 7 (CLCN7, Accession NM\_001287) is a VGAM623 host target gene. CLCN7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLCN7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLCN7 BINDING SITE, designated SEQ ID:6963, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26106] A function of VGAM623 is therefore inhibition of Chloride Channel 7 (CLCN7, Accession NM\_001287), a gene which is voltage-gated chloride channel. Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCN7. The function of CLCN7 has been established by previous

studies. Cleiren et al. (2001) reported 7 different mutations in the CLCN7 gene among 12 autosomal dominant osteopetrosis type II (OPTA2; 166600) families analyzed. Among these families was the Danish family initially linked to chromosome 1p21. Additionally, 1 patient with the severe autosomal recessive infantile form of osteopetrosis (OPTB1) was identified as being homozygous for a CLCN7 mutation. The authors hypothesized that OPTA2 reflects a dominant negative effect, since loss-of-function mutations in CLCN7 do not cause abnormalities in heterozygous individuals. Because some OPTB1 patients have mutations in both copies of the CLCN7 gene, it appears that OPTA2 is allelic with a subset of OPTB1 cases. In a patient with autosomal recessive infantile malignant osteopetrosis (OMIM Ref. No. 259700), Kornak et al. (2001) identified compound heterozygosity for a C-to-T transition at codon 555 of the CLCN7 gene, leading to gln-to-ter substitution, and a G-to-A transition at nucleotide 2285, leading to an arg762-to-gln substitution (602727.0002). The arg762-to-gln substitution abolished a positive charge within the conserved CBS2 domain of CCLN7. To investigate whether the mutations affected protein expression, fibroblasts were analyzed by Western



blot analysis and immunofluorescence. In contrast to control cells, CLCN7 protein could not be detected in the fibroblasts from the patient. Animal model experiments lend further support to the function of CLCN7. Kornak et al. (2001) observed that mice with targeted disruption of the *Clcn7* gene (*Clcn7*  $-/-$ ) had severe osteopetrosis and retinal degeneration. Although osteoclasts were present in normal numbers, they failed to resorb bone because they could not acidify the extracellular resorption lacuna. *Clcn7* was found to reside in late endosomal and lysosomal compartments. In osteoclasts it was highly expressed in the ruffled membrane, formed by the fusion of H(+) ATPase-containing vesicles, that secretes protons into the lacuna. Based on the similarity between the mouse model and human infantile malignant osteopetrosis (OMIM Ref. No. 259700), Kornak et al. (2001) searched for mutations in the human CLCN7 gene in patients with the disease. They identified CLCN7 mutations in 1 of 12 patients with infantile malignant osteopetrosis. The authors concluded that CLCN7 provides the chloride conductance required for an efficient proton pumping by the H(+) ATPase of the osteoclast ruffled membrane.

[26107] It is appreciated that the abovementioned animal model

for CLCN7 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[26108] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26109] Cleiren, E.; Benichou, O.; Van Hul, E.; Gram, J.; Bollerslav, J.; Singer, F. R.; Beaverson, K.; Aledo, A.; Whyte, M. P.; Yoneyama, T.; deVernejou, M.-C.; Van Hul, W. : Albers-Schonberg disease (autosomal dominant osteopetrosis, type II) results from mutations in the CLCN7 chloride channel gene. Hum. Molec. Genet. 10: 2861-2867, 2001.  
; and

[26110] Kornak, U.; Kasper, D.; Bosl, M. R.; Kaiser, E.; Schweizer, M.; Schulz, A.; Friedrich, W.; Delling, G.; Jentsch, T. J. : Loss of the ClC-7 chloride channel leads to osteopetrosis in mi.

[26111] Further studies establishing the function and utilities of CLCN7 are found in John Hopkins OMIM database record ID 602727, and in cited publications numbered 8588, 859 and 11076 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. N-acetylgalactosaminidase, Alpha- (NAGA, Acces-

sion NM\_000262) is another VGAM623 host target gene. NAGA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NAGA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAGA BINDING SITE, designated SEQ ID:5798, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26112] Another function of VGAM623 is therefore inhibition of N-acetylgalactosaminidase, Alpha- (NAGA, Accession NM\_000262). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAGA. PDGFA Associated Protein 1 (PDAP1, Accession XM\_166484) is another VGAM623 host target gene. PDAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDAP1 BINDING SITE, designated SEQ ID:44420, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3334.

[26113] Another function of VGAM623 is therefore inhibition of PDGFA Associated Protein 1 (PDAP1, Accession XM\_166484). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDAP1. Stanniocalcin 1 (STC1, Accession NM\_003155) is another VGAM623 host target gene. STC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STC1 BINDING SITE, designated SEQ ID:9133, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26114] Another function of VGAM623 is therefore inhibition of Stanniocalcin 1 (STC1, Accession NM\_003155), a gene which stimulates renal phosphate reabsorption, and could therefore prevent hypercalcemia. Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STC1. The function of STC1 has been established by previous stud-

ies. Stanniocalcin (STC) is a calcium-regulated hormone in bony fishes. The hormone was so named because it is synthesized by the corpuscles of Stannius, endocrine glands that are associated with the kidneys of all fishes with a bony skeleton. The primary function of STC in fishes is the prevention of hypercalcemia; Olsen et al. (1996) noted that a rise in serum calcium levels is the primary stimulus for secretion. Upon release into the circulation, STC lowers calcium transport by the gills, thereby reducing its rate of influx from the environment into the extracellular compartment. A second equally important action of STC is stimulation of phosphate reabsorption by renal proximal tubules. The consequence of this renal effect is increased levels of plasma phosphate, which combines with excess calcium and promotes its disposal into bone and scales. Wagner et al. (1995) found evidence of STC immunoreactivity in human kidney and serum, suggesting the existence of the hormone in mammals. Olsen et al. (1996) isolated a human cDNA clone encoding the mammalian homolog of STC. Human STC was found to be 247 amino acids long and to share 73% amino acid sequence similarity with fish STC. Polyclonal antibodies to recombinant human STC localized to a distinct cell type in

the nephron tubule, suggesting kidney as a possible site of synthesis. Recombinant human STC inhibited the gill transport of calcium when administered to fish and stimulated renal phosphate reabsorption in the rat.

[26115] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26116] Olsen, H. S.; Cepeda, M. A.; Zhang, Q.-Q.; Rosen, C. A.; Vozzolo, B. L.; Wagner, G. F. : Human stanniocalcin: a possible hormonal regulator of mineral metabolism. *Proc. Nat. Acad. Sci.* 93: 1792–1796, 1996. ; and

[26117] Wagner, G. F.; Guiraudon, C. C.; Milliken, C.; Copp, D. H. : Immunological and biological evidence for a stanniocalcin-like hormone in human kidney. *Proc. Nat. Acad. Sci.* 92: 1871–1875.

[26118] Further studies establishing the function and utilities of STC1 are found in John Hopkins OMIM database record ID 601185, and in cited publications numbered 9509–9514, 963 and 9834 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Surfeit 5 (SURF5, Accession NM\_006752) is another VGAM623 host target gene. SURF5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by SURF5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SURF5 BINDING SITE, designated SEQ ID:13606, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26119] Another function of VGAM623 is therefore inhibition of Surfeit 5 (SURF5, Accession NM\_006752). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SURF5. Chromosome 11 Open Reading Frame 14 (C11orf14, Accession NM\_020645) is another VGAM623 host target gene. C11orf14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C11orf14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C11orf14 BINDING SITE, designated SEQ ID:21808, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26120] Another function of VGAM623 is therefore inhibition of

Chromosome 11 Open Reading Frame 14 (C11orf14, Accession NM\_020645). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C11orf14. ERp44 (Accession XM\_088476) is another VGAM623 host target gene. ERp44 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ERp44, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ERp44 BINDING SITE, designated SEQ ID:39723, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26121] Another function of VGAM623 is therefore inhibition of ERp44 (Accession XM\_088476). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ERp44. KIAA1091 (Accession XM\_045750) is another VGAM623 host target gene. KIAA1091 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1091, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or



BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1091 BINDING SITE, designated SEQ ID:34538, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26122] Another function of VGAM623 is therefore inhibition of KIAA1091 (Accession XM\_045750). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1091. Proteasome (prosome, macropain) Inhibitor Subunit 1 (PI31) (PSMF1, Accession NM\_006814) is another VGAM623 host target gene. PSMF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSMF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSMF1 BINDING SITE, designated SEQ ID:13687, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26123] Another function of VGAM623 is therefore inhibition of Proteasome (prosome, macropain) Inhibitor Subunit 1 (PI31) (PSMF1, Accession NM\_006814). Accordingly, utili-

ties of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSMF1. RAB6C, Member RAS Oncogene Family (RAB6C, Accession NM\_032144) is another VGAM623 host target gene. RAB6C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB6C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB6C BINDING SITE, designated SEQ ID:25832, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26124] Another function of VGAM623 is therefore inhibition of RAB6C, Member RAS Oncogene Family (RAB6C, Accession NM\_032144). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB6C. WD Repeat Domain 9 (WDR9, Accession NM\_033656) is another VGAM623 host target gene. WDR9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WDR9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WDR9 BINDING SITE, designated SEQ ID:27389, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26125] Another function of VGAM623 is therefore inhibition of WD Repeat Domain 9 (WDR9, Accession NM\_033656). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WDR9. LOC143943 (Accession XM\_096504) is another VGAM623 host target gene. LOC143943 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC143943, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143943 BINDING SITE, designated SEQ ID:40381, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26126] Another function of VGAM623 is therefore inhibition of LOC143943 (Accession XM\_096504). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC143943. LOC147976 (Accession XM\_085980) is another VGAM623 host target gene. LOC147976 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147976, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147976 BINDING SITE, designated SEQ ID:38426, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26127] Another function of VGAM623 is therefore inhibition of LOC147976 (Accession XM\_085980). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147976. LOC150157 (Accession XM\_097823) is another VGAM623 host target gene. LOC150157 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150157, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150157 BINDING SITE, designated SEQ ID:41141, to the nucleotide sequence of VGAM623 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3334.

[26128] Another function of VGAM623 is therefore inhibition of LOC150157 (Accession XM\_097823). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150157. LOC157653 (Accession XM\_088353) is another VGAM623 host target gene. LOC157653 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157653, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157653 BINDING SITE, designated SEQ ID:39631, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26129] Another function of VGAM623 is therefore inhibition of LOC157653 (Accession XM\_088353). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157653. LOC256158 (Accession XM\_175125) is another VGAM623 host target gene. LOC256158 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256158, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256158 BINDING SITE, designated SEQ ID:46635, to the nucleotide sequence of VGAM623 RNA, herein designated VGAM RNA, also designated SEQ ID:3334.

[26130] Another function of VGAM623 is therefore inhibition of LOC256158 (Accession XM\_175125). Accordingly, utilities of VGAM623 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256158. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 624 (VGAM624) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26131] VGAM624 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM624 was detected is described hereinabove with reference to Figs. 1–8.

[26132] VGAM624 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C.

VGAM624 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26133] VGAM624 gene encodes a VGAM624 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM624 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM624 precursor RNA is designated SEQ ID:610, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:610 is located at position 4971 relative to the genome of Hepatitis GB Virus C.

[26134] VGAM624 precursor RNA folds onto itself, forming VGAM624 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26135] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM624 folded precursor RNA into VGAM624 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM624 RNA is designated SEQ ID:3335, and is provided hereinbelow with reference to the sequence listing part.

[26136] VGAM624 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM624 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM624 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26137] VGAM624 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM624 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-



cleotide sequence of VGAM624 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM624 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM624 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26138] The complementary binding of VGAM624 RNA, herein designated VGAM RNA, to host target binding sites on VGAM624 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM624 host target RNA into VGAM624 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26139] It is appreciated that VGAM624 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM624 host target genes. The mRNA of each one of this plurality of VGAM624 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM624 RNA, herein designated VGAM RNA, and which when bound by VGAM624 RNA causes inhibition of translation of respective one or more VGAM624 host target proteins.

[26140] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM624 gene, herein designated VGAM GENE, on one or more VGAM624 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26141] It is yet further appreciated that a function of VGAM624 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM624 correlate with, and may be deduced from, the identity of the host target genes which VGAM624 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26142] Nucleotide sequences of the VGAM624 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM624 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM624 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM624 are further described hereinbelow with reference to Table 1.

- [26143] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM624 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM624 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [26144] As mentioned hereinabove with reference to Fig. 1, a function of VGAM624 gene, herein designated VGAM is inhibition of expression of VGAM624 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM624 correlate with, and may be deduced from, the identity of the target genes which VGAM624 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [26145] Carbonic Anhydrase II (CA2, Accession NM\_000067) is a VGAM624 host target gene. CA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CA2 BINDING SITE, designated SEQ ID:5513, to the nucleotide sequence of

VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26146] A function of VGAM624 is therefore inhibition of Carbonic Anhydrase II (CA2, Accession NM\_000067). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CA2. Galactosylceramidase (Krabbe disease) (GALC, Accession NM\_000153) is another VGAM624 host target gene. GALC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GALC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GALC BINDING SITE, designated SEQ ID:5662, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26147] Another function of VGAM624 is therefore inhibition of Galactosylceramidase (Krabbe disease) (GALC, Accession NM\_000153), a gene which hydrolyses the galactose ester bonds of galactosylceramide, galactosylsphingosine, lactosylceramide, and monogalactosyldiglyceride. Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with GALC. The function of GALC has been established by previous studies. Sakai et al. (1994) identified a glu369-to-ter nonsense mutation in a patient with typical Krabbe disease (606890.0001). Rafi et al. (1995) described a mutation of the GALC gene leading to the loss of exons 11–17. The deletion was associated with a C-to-T transition at position 502 of the cDNA leading to replacement of arginine by cysteine; see 606890.0002. Expression of the 502/del mutation in COS-1 cells resulted in no measurable GALC activity above that in mock transfected cells. Rafi et al. (1995) indicated that, while not yet confirmed by expression studies, 3 missense mutations and 1 single nucleotide insertion had been identified in patients with infantile Krabbe disease. Animal model experiments lend further support to the function of GALC. Victoria et al. (1996) found that the disease-causing mutation in the canine GALC gene was demonstrated to be an A-to-C transversion at cDNA position 473 (Y158S). Luzi et al. (1997) found that the mutation causing GLD in the rhesus monkey was a deletion of AC corresponding to cDNA positions 387 and 388 in exon 4. This resulted in a frameshift and stop codon after 46 nucleotides. Using an engineered sense primer and an antisense primer from in-

tron 4, Luzi et al. (1997) developed a rapid method to detect the GALC mutation. When 45 monkeys from 1 colony were tested, 22 were found to be carriers. The availability of this nonhuman primate model of GLD provides unique opportunities to evaluate treatment for this severe disease.

[26148] It is appreciated that the abovementioned animal model for GALC is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[26149] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26150] Rafi, M. A.; Luzi, P.; Chen, Y. Q.; Wenger, D. A. : A large deletion together with a point mutation in the GALC gene is a common mutant allele in patients with infantile Krabbe disease. Hum. Molec. Genet. 4: 1285–1289, 1995.  
; and

[26151] Victoria, T.; Rafi, M. A.; Wenger, D. A. : Cloning of the canine GALC cDNA and identification of the mutation causing globoid cell leukodystrophy in West Highland White and Cairn terrie.

[26152] Further studies establishing the function and utilities of

GALC are found in John Hopkins OMIM database record ID 606890, and in cited publications numbered 9217–5396, 9218–9219, 5397–5401, 9230, 9594–923 and 9590–9593 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphoinositide–3–kinase, Regulatory Subunit, Polypeptide 3 (p55, gamma) (PIK3R3, Accession XM\_027982) is another VGAM624 host target gene. PIK3R3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PIK3R3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIK3R3 BINDING SITE, designated SEQ ID:30604, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26153] Another function of VGAM624 is therefore inhibition of Phosphoinositide–3–kinase, Regulatory Subunit, Polypeptide 3 (p55, gamma) (PIK3R3, Accession XM\_027982). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIK3R3. Protein Tyrosine Phosphatase, Re–



ceptor Type, C (PTPRC, Accession NM\_002838) is another VGAM624 host target gene. PTPRC BINDING SITE1 and PTPRC BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PTPRC, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPRC BINDING SITE1 and PTPRC BINDING SITE2, designated SEQ ID:8721 and SEQ ID:28147 respectively, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26154] Another function of VGAM624 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_002838). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRC. ABLIM (Accession NM\_006720) is another VGAM624 host target gene. ABLIM BINDING SITE1 and ABLIM BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABLIM, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABLIM BINDING SITE1

and ABLIM BINDING SITE2, designated SEQ ID:13547 and SEQ ID:8114 respectively, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26155] Another function of VGAM624 is therefore inhibition of ABLIM (Accession NM\_006720). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABLIM. DKFZP564A1164 (Accession XM\_048304) is another VGAM624 host target gene. DKFZP564A1164 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZP564A1164, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564A1164 BINDING SITE, designated SEQ ID:35153, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26156] Another function of VGAM624 is therefore inhibition of DKFZP564A1164 (Accession XM\_048304). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with DKFZP564A1164. DKFZP564K0822 (Accession XM\_168378) is another VGAM624 host target gene. DKFZP564K0822 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP564K0822, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564K0822 BINDING SITE, designated SEQ ID:45141, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26157] Another function of VGAM624 is therefore inhibition of DKFZP564K0822 (Accession XM\_168378). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564K0822. FLJ14735 (Accession NM\_032832) is another VGAM624 host target gene. FLJ14735 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14735, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14735 BINDING SITE, designated SEQ ID:26609, to the

nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26158] Another function of VGAM624 is therefore inhibition of FLJ14735 (Accession NM\_032832). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14735. G4 (Accession XM\_165712) is another VGAM624 host target gene. G4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by G4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of G4 BINDING SITE, designated SEQ ID:43734, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26159] Another function of VGAM624 is therefore inhibition of G4 (Accession XM\_165712). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with G4. Potassium Inwardly-rectifying Channel, Subfamily J, Member 14 (KCNJ14, Accession NM\_013348) is another VGAM624 host target gene. KCNJ14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by KCNJ14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNJ14 BINDING SITE, designated SEQ ID:14994, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26160] Another function of VGAM624 is therefore inhibition of Potassium Inwardly-rectifying Channel, Subfamily J, Member 14 (KCNJ14, Accession NM\_013348). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNJ14. KIAA0470 (Accession NM\_014812) is another VGAM624 host target gene. KIAA0470 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0470, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0470 BINDING SITE, designated SEQ ID:16776, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26161] Another function of VGAM624 is therefore inhibition of

KIAA0470 (Accession NM\_014812). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0470. PRSC (Accession NM\_006587) is another VGAM624 host target gene. PRSC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRSC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRSC BINDING SITE, designated SEQ ID:13349, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26162] Another function of VGAM624 is therefore inhibition of PRSC (Accession NM\_006587). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRSC. Serum Response Factor (c-fos serum response element-binding transcription factor) (SRF, Accession NM\_003131) is another VGAM624 host target gene. SRF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SRF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRF BINDING SITE, designated SEQ ID:9100, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26163] Another function of VGAM624 is therefore inhibition of Serum Response Factor (c-fos serum response element-binding transcription factor) (SRF, Accession NM\_003131). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRF. Transmembrane 4 Superfamily Member 11 (plasmolipin) (TM4SF11, Accession NM\_015993) is another VGAM624 host target gene. TM4SF11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TM4SF11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TM4SF11 BINDING SITE, designated SEQ ID:18086, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26164] Another function of VGAM624 is therefore inhibition of Transmembrane 4 Superfamily Member 11 (plasmolipin)

(TM4SF11, Accession NM\_015993). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TM4SF11. TRIP-Br2 (Accession NM\_014755) is another VGAM624 host target gene. TRIP-Br2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIP-Br2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIP-Br2 BINDING SITE, designated SEQ ID:16485, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26165] Another function of VGAM624 is therefore inhibition of TRIP-Br2 (Accession NM\_014755). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIP-Br2. Ubiquitination Factor E4B (UFD2 homolog, yeast) (UBE4B, Accession NM\_006048) is another VGAM624 host target gene. UBE4B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE4B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.



Table 2 illustrates the complementarity of the nucleotide sequences of UBE4B BINDING SITE, designated SEQ ID:12682, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26166] Another function of VGAM624 is therefore inhibition of Ubiquitination Factor E4B (UFD2 homolog, yeast) (UBE4B, Accession NM\_006048). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE4B. LOC115219 (Accession XM\_055499) is another VGAM624 host target gene. LOC115219 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115219, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115219 BINDING SITE, designated SEQ ID:36280, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26167] Another function of VGAM624 is therefore inhibition of LOC115219 (Accession XM\_055499). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC115219. LOC126526 (Accession XM\_059053) is another VGAM624 host target gene. LOC126526 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC126526, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126526 BINDING SITE, designated SEQ ID:36846, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26168] Another function of VGAM624 is therefore inhibition of LOC126526 (Accession XM\_059053). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126526. LOC143286 (Accession XM\_096412) is another VGAM624 host target gene. LOC143286 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC143286, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143286 BINDING SITE, designated SEQ ID:40355, to

the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26169] Another function of VGAM624 is therefore inhibition of LOC143286 (Accession XM\_096412). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143286. LOC165693 (Accession XM\_093373) is another VGAM624 host target gene. LOC165693 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC165693, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC165693 BINDING SITE, designated SEQ ID:40187, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26170] Another function of VGAM624 is therefore inhibition of LOC165693 (Accession XM\_093373). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC165693. LOC220020 (Accession XM\_167821) is another VGAM624 host target gene. LOC220020 BINDING SITE is HOST TARGET binding site found in the 5` un-

translated region of mRNA encoded by LOC220020, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220020 BINDING SITE, designated SEQ ID:44865, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26171] Another function of VGAM624 is therefore inhibition of LOC220020 (Accession XM\_167821). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220020. LOC220766 (Accession XM\_165471) is another VGAM624 host target gene. LOC220766 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220766, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220766 BINDING SITE, designated SEQ ID:43651, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26172] Another function of VGAM624 is therefore inhibition of LOC220766 (Accession XM\_165471). Accordingly, utilities

of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220766. LOC254826 (Accession XM\_173188) is another VGAM624 host target gene. LOC254826 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254826 BINDING SITE, designated SEQ ID:46434, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26173] Another function of VGAM624 is therefore inhibition of LOC254826 (Accession XM\_173188). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254826. LOC257554 (Accession XM\_175149) is another VGAM624 host target gene. LOC257554 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257554, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC257554 BINDING SITE, designated SEQ ID:46641, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26174] Another function of VGAM624 is therefore inhibition of LOC257554 (Accession XM\_175149). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257554. LOC92568 (Accession XM\_045852) is another VGAM624 host target gene. LOC92568 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92568, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92568 BINDING SITE, designated SEQ ID:34573, to the nucleotide sequence of VGAM624 RNA, herein designated VGAM RNA, also designated SEQ ID:3335.

[26175] Another function of VGAM624 is therefore inhibition of LOC92568 (Accession XM\_045852). Accordingly, utilities of VGAM624 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92568. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 625 (VGAM625) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26176] VGAM625 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM625 was detected is described hereinabove with reference to Figs. 1–8.

[26177] VGAM625 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM625 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26178] VGAM625 gene encodes a VGAM625 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM625 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM625 precursor RNA is designated SEQ ID:611, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:611 is located at position 6632 relative to the genome of Hepati–

tis GB Virus C.

[26179] VGAM625 precursor RNA folds onto itself, forming VGAM625 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26180] An enzyme complex designated DICER COMPLEX, `dices` the VGAM625 folded precursor RNA into VGAM625 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 73%) nucleotide sequence of VGAM625 RNA is designated SEQ ID:3336, and is provided hereinbelow with reference to the sequence listing part.

[26181] VGAM625 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger



RNA, VGAM625 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM625 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26182] VGAM625 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM625 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM625 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM625 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM625 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26183] The complementary binding of VGAM625 RNA, herein designated VGAM RNA, to host target binding sites on VGAM625 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM625 host target RNA into VGAM625 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26184] It is appreciated that VGAM625 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM625 host target genes. The mRNA of each one of this plurality of VGAM625 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM625 RNA, herein designated VGAM RNA, and which when bound by VGAM625 RNA causes inhibition of translation of respective one or more VGAM625 host target proteins.

[26185] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM625 gene, herein designated VGAM GENE, on one or more VGAM625 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26186] It is yet further appreciated that a function of VGAM625 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM625 cor-

relate with, and may be deduced from, the identity of the host target genes which VGAM625 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26187] Nucleotide sequences of the VGAM625 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM625 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM625 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM625 are further described hereinbelow with reference to Table 1.

[26188] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM625 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM625 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26189] As mentioned hereinabove with reference to Fig. 1, a function of VGAM625 gene, herein designated VGAM is inhibition of expression of VGAM625 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM625 correlate with, and may be deduced

from, the identity of the target genes which VGAM625 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26190] Aryl-hydrocarbon Receptor Nuclear Translocator 2 (ARNT2, Accession NM\_014862) is a VGAM625 host target gene. ARNT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARNT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARNT2 BINDING SITE, designated SEQ ID:16934, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26191] A function of VGAM625 is therefore inhibition of Aryl-hydrocarbon Receptor Nuclear Translocator 2 (ARNT2, Accession NM\_014862), a gene which specifically recognizes the xenobiotic response element (xre). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARNT2. The function of ARNT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with

reference to VGAM345.Otoferlin (OTOF, Accession NM\_004802) is another VGAM625 host target gene. OTOF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OTOF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OTOF BINDING SITE, designated SEQ ID:11224, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26192] Another function of VGAM625 is therefore inhibition of Otoferlin (OTOF, Accession NM\_004802), a gene which is involved in vesicle membrane fusion and required for inner ear function. Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OTOF. The function of OTOF has been established by previous studies. Using a candidate gene approach, Yasunaga et al. (1999) identified a novel human gene, which they called OTOF, mutation in which causes DFNB9 (OMIM Ref. No. 601071). DFNB9 had been linked to chromosome 2p23.1, between D2S2303 and D2S174. Yasunaga et al. (1999) refined the interval to a 1-cM interval between D2S158 and D2S174.

A contig of YACs, BACs, and PACs was constructed, and 2 genes, HADHB and CENPA, and 4 ESTs were assigned to the interval. The genes were excluded as candidates for DFNB9 by function. The ESTs were submitted to rounds of 5-prime RACE-PCR and the deduced amino acids were compared with clones isolated from 2 subtracted mouse cochlear cDNA libraries. The human OTOF gene encodes a 4,954-bp transcript with a 3,690-bp open reading frame and a 1,038-bp 3-prime untranslated region with a polyadenylation signal at position 4934. The 1,230-amino acid protein has a calculated molecular mass of 140.5 kD. It has 3 C2 domains and a single carboxy-terminal trans-membrane domain. The protein is homologous to the *C. elegans* spermatogenesis factor FER-1 and human dysferlin (OMIM Ref. No. 603009), prompting the authors to name it 'otoferlin.' The homology suggests the otoferlin is involved in vesicle membrane fusion. The OTOF gene extends over 21 kb and contains 28 coding exons and a 5-prime untranslated region exon. Otof expression was identified by RT-PCR in mouse cochlea, vestibule, and brain. By in situ hybridization, Otof labeling was seen in the inner hair cells, and faintly in the outer hair cells and spiral ganglion cells, at embryonic day 19.5, P0, and P2.

Neuroepithelia of the utricle, saccule, and semicircular canals expressed Otof during the same days. Type I cells, but not type II cells or supporting cells, expressed Otof. By Northern blot analysis, Yasunaga et al. (2000) detected a 7-kb otoferlin mRNA in the human brain. They isolated a corresponding cDNA, which was predicted to encode a 1,977-long form of otoferlin with 6 C2 domains. They found that the human OTOF gene contains 48 coding exons and spans approximately 90 kb. Other alternatively spliced transcripts were detected, which predicted several long isoforms (with 6 C2 domains) in humans and mice and short isoforms (3 C2 domains) only in humans. Yasunaga et al. (2000) studied a consanguineous family originating from India in which 3 sibs suffered from severe to profound hearing loss. By segregation analysis with polymorphic markers of the DFNB9 chromosomal region, they concluded that an OTOF mutation was likely to underlie deafness in this family. By sequencing the 48 OTOF coding exons in members of this family, they identified a splice mutation in intron 8 (603681.0002). These studies demonstrated that the long otoferlin isoforms are

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[26193] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26194] Yasunaga, S.; Grati, M.; Chardenoux, S.; Smith, T. N.; Friedman, T. B.; Lalwani, A. K.; Wilcox, E. R.; Petit, C. : OTOF encodes multiple long and short isoforms: genetic

evidence that the long ones underlie recessive deafness  
DFNB9. Am. J. Hum. Genet. 67: 591–600, 2000. ; and

[26195] Yasunaga, S.; Grati, M.; Cohen–Salmon, M.; El–Amraoui, A.; Mustapha, M.; Salem, N.; El–Zir, E.; Loiselet, J.; Petit, C. : A mutation in OTOF, encoding otoferlin, a FER–1–like protein, c.

[26196] Further studies establishing the function and utilities of OTOF are found in John Hopkins OMIM database record ID 603681, and in cited publications numbered 8486–8487, 786 and 8488 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Regulator of G–protein Signalling 3 (RGS3, Accession NM\_134427) is another VGAM625 host target gene. RGS3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RGS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RGS3 BINDING SITE, designated SEQ ID:28669, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26197] Another function of VGAM625 is therefore inhibition of Regulator of G–protein Signalling 3 (RGS3, Accession

NM\_134427), a gene which negatively regulates G protein-coupled receptor signalling. Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RGS3. The function of RGS3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM404. Transcription Factor 7 (T-cell specific, HMG-box) (TCF7, Accession NM\_003202) is another VGAM625 host target gene. TCF7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TCF7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCF7 BINDING SITE, designated SEQ ID:9194, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26198] Another function of VGAM625 is therefore inhibition of Transcription Factor 7 (T-cell specific, HMG-box) (TCF7, Accession NM\_003202). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCF7. ABLIM

(Accession NM\_002313) is another VGAM625 host target gene. ABLIM BINDING SITE1 and ABLIM BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABLIM, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABLIM BINDING SITE1 and ABLIM BINDING SITE2, designated SEQ ID:8115 and SEQ ID:13548 respectively, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26199] Another function of VGAM625 is therefore inhibition of ABLIM (Accession NM\_002313). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABLIM. DKFZP564L0864 (Accession XM\_051905) is another VGAM625 host target gene. DKFZP564L0864 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564L0864, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564L0864 BINDING SITE, designated

SEQ ID:35920, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26200] Another function of VGAM625 is therefore inhibition of DKFZP564L0864 (Accession XM\_051905). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564L0864. FLJ12552 (Accession NM\_022832) is another VGAM625 host target gene. FLJ12552 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12552, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12552 BINDING SITE, designated SEQ ID:23114, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26201] Another function of VGAM625 is therefore inhibition of FLJ12552 (Accession NM\_022832). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12552. FLJ22390 (Accession NM\_022746) is another VGAM625 host target gene. FLJ22390 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ22390, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22390 BINDING SITE, designated SEQ ID:22958, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26202] Another function of VGAM625 is therefore inhibition of FLJ22390 (Accession NM\_022746). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22390. KIAA0210 (Accession NM\_014744) is another VGAM625 host target gene. KIAA0210 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0210, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0210 BINDING SITE, designated SEQ ID:16422, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26203] Another function of VGAM625 is therefore inhibition of

KIAA0210 (Accession NM\_014744). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0210. Nuclear Receptor Subfamily 1, Group I, Member 3 (NR1I3, Accession NM\_005122) is another VGAM625 host target gene. NR1I3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by NR1I3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR1I3 BINDING SITE, designated SEQ ID:11605, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26204] Another function of VGAM625 is therefore inhibition of Nuclear Receptor Subfamily 1, Group I, Member 3 (NR1I3, Accession NM\_005122). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR1I3. Sema Domain, Transmembrane Domain (TM), and Cytoplasmic Domain, (semaphorin) 6B (SEMA6B, Accession NM\_032108) is another VGAM625 host target gene. SEMA6B BINDING SITE is HOST TARGET binding site found in the 3` untranslated

region of mRNA encoded by SEMA6B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA6B BINDING SITE, designated SEQ ID:25800, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26205] Another function of VGAM625 is therefore inhibition of Sema Domain, Transmembrane Domain (TM), and Cytoplasmic Domain, (semaphorin) 6B (SEMA6B, Accession NM\_032108). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA6B. SV2 (Accession NM\_014849) is another VGAM625 host target gene. SV2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SV2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SV2 BINDING SITE, designated SEQ ID:16884, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26206] Another function of VGAM625 is therefore inhibition of



SV2 (Accession NM\_014849). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SV2.

LOC133814 (Accession XM\_068546) is another VGAM625 host target gene. LOC133814 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC133814, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133814 BINDING SITE, designated SEQ ID:37381, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26207] Another function of VGAM625 is therefore inhibition of LOC133814 (Accession XM\_068546). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133814. LOC146227 (Accession XM\_085374) is another VGAM625 host target gene. LOC146227 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146227, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC146227 BINDING SITE, designated SEQ ID:38088, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26208] Another function of VGAM625 is therefore inhibition of LOC146227 (Accession XM\_085374). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146227. LOC152674 (Accession XM\_098251) is another VGAM625 host target gene. LOC152674 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152674, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152674 BINDING SITE, designated SEQ ID:41539, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26209] Another function of VGAM625 is therefore inhibition of LOC152674 (Accession XM\_098251). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152674. LOC197287 (Accession XM\_027541) is an-

other VGAM625 host target gene. LOC197287 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197287, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197287 BINDING SITE, designated SEQ ID:30522, to the nucleotide sequence of VGAM625 RNA, herein designated VGAM RNA, also designated SEQ ID:3336.

[26210] Another function of VGAM625 is therefore inhibition of LOC197287 (Accession XM\_027541). Accordingly, utilities of VGAM625 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197287. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 626 (VGAM626) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26211] VGAM626 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM626 was detected is described

hereinabove with reference to Figs. 1–8.

[26212] VGAM626 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C.

VGAM626 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26213] VGAM626 gene encodes a VGAM626 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM626 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM626 precursor RNA is designated SEQ ID:612, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:612 is located at position 1889 relative to the genome of Hepatitis GB Virus C.

[26214] VGAM626 precursor RNA folds onto itself, forming VGAM626 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[26215] An enzyme complex designated DICER COMPLEX, `dices` the VGAM626 folded precursor RNA into VGAM626 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM626 RNA is designated SEQ ID:3337, and is provided hereinbelow with reference to the sequence listing part.

[26216] VGAM626 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM626 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM626 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26217] VGAM626 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM626 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM626 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM626 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM626 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26218] The complementary binding of VGAM626 RNA, herein designated VGAM RNA, to host target binding sites on VGAM626 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM626 host target RNA into VGAM626 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26219] It is appreciated that VGAM626 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM626 host target genes. The mRNA of each one of this plurality of VGAM626 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM626 RNA, herein designated VGAM RNA, and which when bound by VGAM626 RNA causes inhibition of translation of respective one or more VGAM626 host target proteins.

[26220] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM626 gene, herein designated VGAM GENE, on one or more VGAM626 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26221] It is yet further appreciated that a function of VGAM626 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM626 correlate with, and may be deduced from, the identity of the host target genes which VGAM626 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26222] Nucleotide sequences of the VGAM626 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM626 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding



of VGAM626 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM626 are further described hereinbelow with reference to Table 1.

[26223] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM626 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM626 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26224] As mentioned hereinabove with reference to Fig. 1, a function of VGAM626 gene, herein designated VGAM is inhibition of expression of VGAM626 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM626 correlate with, and may be deduced from, the identity of the target genes which VGAM626 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26225] Adrenergic, Beta, Receptor Kinase 1 (ADRBK1, Accession NM\_001619) is a VGAM626 host target gene. ADRBK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADRBK1, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADRBK1 BINDING SITE, designated SEQ ID:7328, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26226] A function of VGAM626 is therefore inhibition of Adrenergic, Beta, Receptor Kinase 1 (ADRBK1, Accession NM\_001619), a gene which regulates desensitization of  $\beta$ -adrenergic receptors and related GPCRs. Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADRBK1. The function of ADRBK1 has been established by previous studies. Beta-adrenergic receptor kinase (BARK) phosphorylates the  $\beta$ -2-adrenergic receptor (OMIM Ref. No. 109690) and appears to mediate agonist-specific desensitization observed at high agonist concentrations. BARK is a ubiquitous cytosolic enzyme that specifically phosphorylates the activated form of the  $\beta$ -adrenergic and related G protein-coupled receptors. Benovic et al. (1991) used the bovine BARK cDNA to screen a human retina library and isolate the human cDNA. They showed that it encodes a protein of 689 amino acids with an over-

all 98% amino acid and 92.5% nucleotide identity with bovine BARK. By study of rodent/human hybrid cells retaining various human chromosomes and parts of chromosomes, Benovic et al. (1991) demonstrated that the ADRBK1 gene segregates with the long arm of chromosome 11, centromeric to 11q13, i.e., 11cen-q13. Benovic et al. (1991) mapped the homologous gene to mouse chromosome 19. Animal model experiments lend further support to the function of ADRBK1. Rockman et al. (1998) mated transgenic mice with cardiac-restricted overexpression of either a peptide inhibitor of beta-ARK1 or the beta-2-AR into a genetic model of murine heart failure. They found that overexpression of the inhibitor prevented the development of cardiomyopathy in this murine model of heart failure.

[26227] It is appreciated that the abovementioned animal model for ADRBK1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[26228] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26229] Benovic, J. L.; Stone, W. C.; Huebner, K.; Croce, C.; Caron,

M. G.; Lefkowitz, R. J. : cDNA cloning and chromosomal localization of the human beta-adrenergic receptor kinase. FEBS Lett. 283: 122–126, 1991. ; and

[26230] Rockman, H. A.; Chien, K. R.; Choi, D.-J.; Iaccarino, G.; Hunter, J. J.; Ross, J., Jr.; Lefkowitz, R. J.; Koch, W. J. : Expression of a beta-adrenergic receptor kinase 1 inhibitor preven.

[26231] Further studies establishing the function and utilities of ADRBK1 are found in John Hopkins OMIM database record ID 109635, and in cited publications numbered 1447–1451 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. 24-dehydrocholesterol Reductase (DHCR24, Accession NM\_014762) is another VGAM626 host target gene. DHCR24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DHCR24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DHCR24 BINDING SITE, designated SEQ ID:16525, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26232] Another function of VGAM626 is therefore inhibition of 24-dehydrocholesterol Reductase (DHCR24, Accession NM\_014762), a gene which catalyzes the reduction of sterol intermediates. Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DHCR24. The function of DHCR24 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM235. Follistatin-like 3 (secreted glycoprotein) (FSTL3, Accession NM\_005860) is another VGAM626 host target gene. FSTL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FSTL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FSTL3 BINDING SITE, designated SEQ ID:12469, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26233] Another function of VGAM626 is therefore inhibition of Follistatin-like 3 (secreted glycoprotein) (FSTL3, Accession NM\_005860), a gene which is a member of the follistatin-module-protein family. Accordingly, utilities of VGAM626

include diagnosis, prevention and treatment of diseases and clinical conditions associated with FSTL3. The function of FSTL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200. Lymphocyte Antigen 6 Complex, Locus E (LY6E, Accession NM\_002346) is another VGAM626 host target gene. LY6E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LY6E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LY6E BINDING SITE, designated SEQ ID:8147, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26234] Another function of VGAM626 is therefore inhibition of Lymphocyte Antigen 6 Complex, Locus E (LY6E, Accession NM\_002346). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LY6E. NADH Dehydrogenase (ubiquinone) Flavoprotein 3, 10kDa (NDUFV3, Accession NM\_021075) is another VGAM626 host target gene. NDUFV3 BINDING SITE is HOST TARGET binding site found

in the 5' untranslated region of mRNA encoded by NDUFV3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDUFV3 BINDING SITE, designated SEQ ID:22044, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26235] Another function of VGAM626 is therefore inhibition of NADH Dehydrogenase (ubiquinone) Flavoprotein 3, 10kDa (NDUFV3, Accession NM\_021075), a gene which transports electrons from NADH to ubiquinone. Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDUFV3. The function of NDUFV3 has been established by previous studies. NADH:ubiquinone oxidoreductase (complex I; EC 1.6.5.3) is an inner mitochondrial membrane-bound multisubunit enzyme complex. Complex I consists of at least 41 subunits of which 7 are encoded by the mitochondrial genome. See MTND1 (OMIM Ref. No. 516000) through MTND6 (OMIM Ref. No. 516006). As one of the complexes of the mitochondrial respiratory chain, complex I functions in the catalysis of

the rotenone-sensitive oxidation of NADH and the reduction of ubiquinone. By means of chaotropic agents, complex I can be resolved into 2 hydrophilic fractions, the flavoprotein fraction and the iron-protein fraction, and a hydrophobic fraction. The flavoprotein fraction comprises the 51-, 24-, and 10-kD subunits, all encoded by the nuclear genes NDUFV1 (OMIM Ref. No. 161015), NDUFV2 (OMIM Ref. No. 600532), and NDUFV3, respectively. This fraction plays a catalytic role in the oxidation of NADH as it is associated with flavoprotein and NAD binding. The 51-kD and 24-kD subunits are involved in electron transfer. The function of the 10-kD protein is unknown. The human gene for the 10-kD flavoprotein subunit was completely cloned and sequenced by de Coo et al. (1997). The NDUFV3 gene was found to contain 3 exons, spanning 20 kb. The open reading frame contains a 34-codon import sequence and a 74-codon mature protein sequence. Its homology to bovine and rat protein sequence was found but not to any other known protein. Northern blot analysis showed that the NDUFV3 gene is ubiquitously expressed. By fluorescence in situ hybridization, de Coo et al. (1997) assigned the NDUFV3 gene to 21q22.3, where it may play a dosage-dependent role in the phenotype of Down syn-



drome (OMIM Ref. No. 190685). Berry et al. (2000) found that NDUFV3 is located approximately 120 kb telomeric to PDE9A (OMIM Ref. No. 602973).

[26236] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26237] Berry, A.; Scott, H. S.; Kudoh, J.; Talior, I.; Korostishevsky, M.; Wattenhofer, M.; Guipponi, M.; Barras, C.; Rossier, C.; Shibuya, K.; Wang, J.; Kawasaki, K.; Asakawa, S.; Minoshima, S.; Shimizu, N.; Antonarakis, S.; Bonne-Tamir, B. : Refined localization of autosomal recessive nonsyndromic deafness DFNB10 locus using 34 novel microsatellite markers, genomic structure, and exclusion of six known genes in the region. *Genomics* 68: 22–29, 2000. ; and

[26238] de Coo, R. F. M.; Buddiger, P.; Smeets, H. J. M.; van Oost, B. A. : Molecular cloning and characterization of the human mitochondrial NADH:oxidoreductase 10-kDa gene (NDUFV3). *Genomics*.

[26239] Further studies establishing the function and utilities of NDUFV3 are found in John Hopkins OMIM database record ID 602184, and in cited publications numbered 786 and 8532 listed in the bibliography section hereinbelow, which

are also hereby incorporated by reference. Upstream Binding Transcription Factor, RNA Polymerase I (UBTF, Accession NM\_014233) is another VGAM626 host target gene. UBTF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBTF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBTF BINDING SITE, designated SEQ ID:15497, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26240] Another function of VGAM626 is therefore inhibition of Upstream Binding Transcription Factor, RNA Polymerase I (UBTF, Accession NM\_014233), a gene which recognizes the ribosomal rna gene promoter and activates transcription. Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBTF. The function of UBTF has been established by previous studies. Upstream binding factor (UBF) is a transcription factor required for expression of the 18S, 5.8S, and 28S ribosomal RNAs, along with SL1 (a complex of TBP (OMIM Ref. No. 600075) and multiple TBP-associated factors or 'TAFs'). Two UBF polypeptides,

of 94 and 97 kD, exist in the human (Bell et al., 1988).

UBF is a nucleolar phosphoprotein with both DNA binding and transactivation domains. Sequence-specific DNA binding to the core and upstream control elements of the human rRNA promoter is mediated through several HMG boxes (Jantzen et al., 1990). Jantzen et al. (1990) cloned human UBF by screening a HeLa cell cDNA library with DNA probes based on tryptic peptides of the protein. They found an open reading frame encoding the 764-amino acid UBF. The authors also characterized DNA binding characteristics of UBF. Chan et al. (1991) cloned the human cDNA by screening an expression library with a specific autoantibody that recognizes nucleolar organizing regions. Jones et al. (1995) mapped the gene, symbolized UBTF, to the BRCA1 region of 17q21 by analyzing genomic clones from that region. They found the gene order to be cen--PPY(OMIM Ref. No.

167780)--UBTF--EPB3(OMIM Ref. No.

109270)--GP2B(OMIM Ref. No. 273800)--tel.

[26241] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26242] Jantzen, H.-M.; Admon, A.; Bell, S. P.; Tjian, R. : Nucleolar

transcription factor hUBF contains a DNA-binding motif with homology to HMG proteins. Nature 344: 830–836, 1990. ; and

[26243] Chan, E. K. L.; Imai, H.; Hamel, J. C.; Tan, E. M. : Human autoantibody to RNA polymerase I transcription factor hUBF: molecular identity of nucleolus organizer region autoantigen NOR-9.

[26244] Further studies establishing the function and utilities of UBTF are found in John Hopkins OMIM database record ID 600673, and in cited publications numbered 1310–1316 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CD109 (Accession NM\_133493) is another VGAM626 host target gene. CD109 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CD109, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD109 BINDING SITE, designated SEQ ID:28571, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26245] Another function of VGAM626 is therefore inhibition of

CD109 (Accession NM\_133493). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD109. DKFZP434N161 (Accession XM\_085920) is another VGAM626 host target gene. DKFZP434N161 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434N161, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434N161 BINDING SITE, designated SEQ ID:38397, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26246] Another function of VGAM626 is therefore inhibition of DKFZP434N161 (Accession XM\_085920). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434N161. FLJ12750 (Accession NM\_024667) is another VGAM626 host target gene. FLJ12750 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of FLJ12750 BINDING SITE, designated SEQ ID:23971, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26247] Another function of VGAM626 is therefore inhibition of FLJ12750 (Accession NM\_024667). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12750. KIAA0346 (Accession XM\_043272) is another VGAM626 host target gene. KIAA0346 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA0346, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0346 BINDING SITE, designated SEQ ID:33920, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26248] Another function of VGAM626 is therefore inhibition of KIAA0346 (Accession XM\_043272). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0346. KIAA1023 (Accession NM\_017604) is another

VGAM626 host target gene. KIAA1023 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1023, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1023 BINDING SITE, designated SEQ ID:19089, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26249] Another function of VGAM626 is therefore inhibition of KIAA1023 (Accession NM\_017604). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1023. KIAA1163 (Accession XM\_086231) is another VGAM626 host target gene. KIAA1163 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1163, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1163 BINDING SITE, designated SEQ ID:38556, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26250] Another function of VGAM626 is therefore inhibition of KIAA1163 (Accession XM\_086231). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1163. KIAA1465 (Accession XM\_027396) is another VGAM626 host target gene. KIAA1465 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1465 BINDING SITE, designated SEQ ID:30503, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26251] Another function of VGAM626 is therefore inhibition of KIAA1465 (Accession XM\_027396). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1465. SCYA14 (Accession NM\_032962) is another VGAM626 host target gene. SCYA14 BINDING SITE1 and SCYA14 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SCYA14, corresponding to HOST TARGET binding sites



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCYA14 BINDING SITE1 and SCYA14 BINDING SITE2, designated SEQ ID:26773 and SEQ ID:10373 respectively, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26252] Another function of VGAM626 is therefore inhibition of SCYA14 (Accession NM\_032962). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCYA14. LOC148697 (Accession XM\_086276) is another VGAM626 host target gene. LOC148697 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148697, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148697 BINDING SITE, designated SEQ ID:38573, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26253] Another function of VGAM626 is therefore inhibition of LOC148697 (Accession XM\_086276). Accordingly, utilities

of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148697. LOC155179 (Accession XM\_088169) is another VGAM626 host target gene. LOC155179 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC155179, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155179 BINDING SITE, designated SEQ ID:39556, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26254] Another function of VGAM626 is therefore inhibition of LOC155179 (Accession XM\_088169). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155179. LOC219700 (Accession XM\_167570) is another VGAM626 host target gene. LOC219700 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC219700 BINDING SITE, designated SEQ ID:44702, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26255] Another function of VGAM626 is therefore inhibition of LOC219700 (Accession XM\_167570). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219700. LOC220753 (Accession XM\_167549) is another VGAM626 host target gene. LOC220753 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220753, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220753 BINDING SITE, designated SEQ ID:44662, to the nucleotide sequence of VGAM626 RNA, herein designated VGAM RNA, also designated SEQ ID:3337.

[26256] Another function of VGAM626 is therefore inhibition of LOC220753 (Accession XM\_167549). Accordingly, utilities of VGAM626 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220753. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 627 (VGAM627) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26257] VGAM627 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM627 was detected is described hereinabove with reference to Figs. 1–8.

[26258] VGAM627 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM627 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26259] VGAM627 gene encodes a VGAM627 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM627 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM627 precursor RNA is designated SEQ ID:613, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:613 is located at position 1443 relative to the genome of Hepati-

tis GB Virus C.

[26260] VGAM627 precursor RNA folds onto itself, forming VGAM627 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26261] An enzyme complex designated DICER COMPLEX, `dices` the VGAM627 folded precursor RNA into VGAM627 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM627 RNA is designated SEQ ID:3338, and is provided hereinbelow with reference to the sequence listing part.

[26262] VGAM627 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM627 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM627 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26263] VGAM627 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM627 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM627 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM627 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM627 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[26264] The complementary binding of VGAM627 RNA, herein designated VGAM RNA, to host target binding sites on VGAM627 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM627 host target RNA into VGAM627 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26265] It is appreciated that VGAM627 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM627 host target genes. The mRNA of each one of this plurality of VGAM627 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM627 RNA, herein designated VGAM RNA, and which when bound by VGAM627 RNA causes inhibition of translation of respective one or more VGAM627 host target proteins.

[26266] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM627 gene, herein designated VGAM GENE, on one or more VGAM627 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26267] It is yet further appreciated that a function of VGAM627 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM627 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM627 cor-



relate with, and may be deduced from, the identity of the host target genes which VGAM627 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26268] Nucleotide sequences of the VGAM627 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM627 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM627 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM627 are further described hereinbelow with reference to Table 1.

[26269] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM627 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM627 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26270] As mentioned hereinabove with reference to Fig. 1, a function of VGAM627 gene, herein designated VGAM is inhibition of expression of VGAM627 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM627 correlate with, and may be deduced

from, the identity of the target genes which VGAM627 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26271] FLJ12294 (Accession NM\_025100) is a VGAM627 host target gene. FLJ12294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12294 BINDING SITE, designated SEQ ID:24744, to the nucleotide sequence of VGAM627 RNA, herein designated VGAM RNA, also designated SEQ ID:3338.

[26272] A function of VGAM627 is therefore inhibition of FLJ12294 (Accession NM\_025100). Accordingly, utilities of VGAM627 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12294. LOC255718 (Accession XM\_174148) is another VGAM627 host target gene. LOC255718 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255718, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of LOC255718 BINDING SITE, designated SEQ ID:46581, to the nucleotide sequence of VGAM627 RNA, herein designated VGAM RNA, also designated SEQ ID:3338.

[26273] Another function of VGAM627 is therefore inhibition of LOC255718 (Accession XM\_174148). Accordingly, utilities of VGAM627 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255718. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 628 (VGAM628) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26274] VGAM628 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM628 was detected is described hereinabove with reference to Figs. 1–8.

[26275] VGAM628 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM628 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[26276] VGAM628 gene encodes a VGAM628 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM628 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM628 precursor RNA is designated SEQ ID:614, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:614 is located at position 3072 relative to the genome of Hepatitis GB Virus C.

[26277] VGAM628 precursor RNA folds onto itself, forming VGAM628 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26278] An enzyme complex designated DICER COMPLEX, `dices` the VGAM628 folded precursor RNA into VGAM628 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM628 RNA is designated SEQ ID:3339, and is provided hereinbelow with reference to the sequence listing part.

[26279] VGAM628 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM628 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM628 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26280] VGAM628 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM628 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM628 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM628 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM628 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26281] The complementary binding of VGAM628 RNA, herein designated VGAM RNA, to host target binding sites on VGAM628 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM628 host target RNA into VGAM628 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26282] It is appreciated that VGAM628 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM628 host target genes. The mRNA of each one of this plurality of VGAM628 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM628 RNA, herein designated VGAM RNA, and which when bound by VGAM628 RNA causes inhibition of translation of respective one or more VGAM628 host target proteins.

[26283] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM628 gene, herein designated VGAM GENE, on one or more VGAM628 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26284] It is yet further appreciated that a function of VGAM628 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM628 correlate with, and may be deduced from, the identity of the host target genes which VGAM628 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26285] Nucleotide sequences of the VGAM628 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM628 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM628 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM628 are further described hereinbelow with reference to Table 1.

[26286] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of



Fig. 1, found on VGAM628 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM628 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26287] As mentioned hereinabove with reference to Fig. 1, a function of VGAM628 gene, herein designated VGAM is inhibition of expression of VGAM628 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM628 correlate with, and may be deduced from, the identity of the target genes which VGAM628 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26288] Hermansky-Pudlak Syndrome 3 (HPS3, Accession NM\_032383) is a VGAM628 host target gene. HPS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HPS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HPS3 BINDING SITE, designated SEQ ID:26176, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26289] A function of VGAM628 is therefore inhibition of Herman-sky-Pudlak Syndrome 3 (HPS3, Accession NM\_032383). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HPS3. MAP-kinase Activating Death Domain (MADD, Accession NM\_130470) is another VGAM628 host target gene. MADD BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MADD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MADD BINDING SITE, designated SEQ ID:28232, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26290] Another function of VGAM628 is therefore inhibition of MAP-kinase Activating Death Domain (MADD, Accession NM\_130470), a gene which may regulate two different pathways for neural activities. interacts with the type-1 tumor necrosis factor receptor (TNFR1); death domain-containing protein. Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MADD. The function of

MADD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM430. Pleckstrin Homology, Sec7 and Coiled/coil Domains 3 (PSCD3, Accession NM\_004227) is another VGAM628 host target gene. PSCD3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSCD3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSCD3 BINDING SITE, designated SEQ ID:10422, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26291] Another function of VGAM628 is therefore inhibition of Pleckstrin Homology, Sec7 and Coiled/coil Domains 3 (PSCD3, Accession NM\_004227), a gene which regulates vesicle trafficking in eukaryotic cells. Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSCD3. The function of PSCD3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference

to VGAM191. Transcription Factor 21 (TCF21, Accession NM\_003206) is another VGAM628 host target gene.

TCF21 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TCF21, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCF21 BINDING SITE, designated SEQ ID:9204, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26292] Another function of VGAM628 is therefore inhibition of Transcription Factor 21 (TCF21, Accession NM\_003206), a gene which may play a role in the specification or differentiation of one or more subsets of epicardial cell types. Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCF21. The function of TCF21 has been established by previous studies. By searching EST databases for class B bHLH proteins expressed in developing kidney, Quaggin et al. (1998) identified human and mouse cDNAs encoding TCF21. They called the protein POD1 because it was highly expressed in podocytes (visceral glomerular epithelial cells). The predicted

179-amino acid human TCF21 protein contains a 57-amino acid bHLH domain, a putative nuclear localization signal, and an acidic transcriptional activation domain. Human TCF21 shares 60% and 95% protein sequence identity with TCF15 (OMIM Ref. No. 601010) and mouse Tcf21, respectively. Northern blot analysis revealed that TCF21 is expressed as a 1.3-kb mRNA in human lung, kidney, heart, and placenta, and at lower levels in pancreas. Animal model experiments lend further support to the function of TCF21. Lu et al. (2000) demonstrated that mice homozygous for a capsulin-null mutation fail to form a spleen. Homozygous mutant embryos expressed Hox11 (OMIM Ref. No. 186770) and Bapx1 (OMIM Ref. No. 602183), which had previously been shown to be essential regulators of spleen organogenesis. However, in the capsulin-null homozygous embryos, the primordium of the spleen failed to develop beyond an initial group of precursor cells and underwent rapid apoptosis. The phenotype of capsulin mutant mice demonstrated that capsulin acts within a subpopulation of splanchnic mesodermal cells to control an essential early step in spleen organogenesis that is likely to represent a point of regulatory convergence of the capsulin, Hox11, and Bapx1 genes.

[26293] It is appreciated that the abovementioned animal model for TCF21 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[26294] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26295] Lu, J.; Chang, P.; Richardson, J. A.; Gan, L.; Weiler, H.; Olson, E. N. : The basic helix-loop-helix transcription factor capsulin controls spleen organogenesis. Proc. Nat. Acad. Sci. 97: 9525-9530, 2000. ; and

[26296] Quaggin, S. E.; Vanden Heuvel, G. B.; Igarashi, P. : Pod-1, a mesoderm-specific basic-helix-loop-helix protein expressed in mesenchymal and glomerular epithelial cells in the developi.

[26297] Further studies establishing the function and utilities of TCF21 are found in John Hopkins OMIM database record ID 603306, and in cited publications numbered 2442-2446 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DJ37E16.5 (Accession NM\_020315) is another VGAM628 host target gene. DJ37E16.5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated

region of mRNA encoded by DJ37E16.5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DJ37E16.5 BINDING SITE, designated SEQ ID:21578, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26298] Another function of VGAM628 is therefore inhibition of DJ37E16.5 (Accession NM\_020315). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DJ37E16.5. DKFZP564O123 (Accession XM\_002810) is another VGAM628 host target gene. DKFZP564O123 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564O123, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564O123 BINDING SITE, designated SEQ ID:29903, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26299] Another function of VGAM628 is therefore inhibition of

DKFZP564O123 (Accession XM\_002810). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564O123. FLJ10761 (Accession NM\_018208) is another VGAM628 host target gene. FLJ10761 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10761, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10761 BINDING SITE, designated SEQ ID:20105, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26300] Another function of VGAM628 is therefore inhibition of FLJ10761 (Accession NM\_018208). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10761. FLJ23189 (Accession NM\_025057) is another VGAM628 host target gene. FLJ23189 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23189, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of FLJ23189 BINDING SITE, designated SEQ ID:24654, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26301] Another function of VGAM628 is therefore inhibition of FLJ23189 (Accession NM\_025057). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23189. NYD-SP11 (Accession NM\_031951) is another VGAM628 host target gene. NYD-SP11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NYD-SP11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP11 BINDING SITE, designated SEQ ID:25692, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26302] Another function of VGAM628 is therefore inhibition of NYD-SP11 (Accession NM\_031951). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP11. SSH2 (Accession XM\_030846) is another VGAM628

host target gene. SSH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSH2 BINDING SITE, designated SEQ ID:31184, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26303] Another function of VGAM628 is therefore inhibition of SSH2 (Accession XM\_030846). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSH2. LOC124976 (Accession XM\_058879) is another VGAM628 host target gene. LOC124976 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC124976, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124976 BINDING SITE, designated SEQ ID:36784, to the nucleotide sequence of VGAM628 RNA, herein designated VGAM RNA, also designated SEQ ID:3339.

[26304] Another function of VGAM628 is therefore inhibition of LOC124976 (Accession XM\_058879). Accordingly, utilities of VGAM628 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124976. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 629 (VGAM629) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26305] VGAM629 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM629 was detected is described hereinabove with reference to Figs. 1–8.

[26306] VGAM629 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM629 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26307] VGAM629 gene encodes a VGAM629 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM629

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM629 precursor RNA is designated SEQ ID:615, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:615 is located at position 7116 relative to the genome of Hepatitis GB Virus C.

[26308] VGAM629 precursor RNA folds onto itself, forming VGAM629 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26309] An enzyme complex designated DICER COMPLEX, `dices` the VGAM629 folded precursor RNA into VGAM629 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 40%) nucleotide sequence of VGAM629 RNA is designated SEQ ID:3340, and is provided hereinbelow with reference to the sequence listing part.

[26310] VGAM629 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM629 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM629 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[26311] VGAM629 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM629 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM629 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM629 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM629 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26312] The complementary binding of VGAM629 RNA, herein designated VGAM RNA, to host target binding sites on VGAM629 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM629 host target RNA into VGAM629 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26313] It is appreciated that VGAM629 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM629 host target genes. The mRNA of each one of this plurality of VGAM629 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM629 RNA, herein designated VGAM RNA, and which when bound by VGAM629 RNA causes inhibition of translation of respective one or more VGAM629 host target proteins.

[26314] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM629 gene, herein designated VGAM GENE, on one or more VGAM629 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26315] It is yet further appreciated that a function of VGAM629 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM629 correlate with, and may be deduced from, the identity of the host target genes which VGAM629 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26316] Nucleotide sequences of the VGAM629 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM629 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM629 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM629 are further described hereinbelow with reference to Table 1.

[26317] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM629 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM629 RNA, herein designated VGAM RNA, are described hereinbelow with refer-



ence to Table 2.

[26318] As mentioned hereinabove with reference to Fig. 1, a function of VGAM629 gene, herein designated VGAM is inhibition of expression of VGAM629 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM629 correlate with, and may be deduced from, the identity of the target genes which VGAM629 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26319] ATPase, Ca++ Transporting, Cardiac Muscle, Slow Twitch 2 (ATP2A2, Accession NM\_001681) is a VGAM629 host target gene. ATP2A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP2A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP2A2 BINDING SITE, designated SEQ ID:7398, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26320] A function of VGAM629 is therefore inhibition of ATPase, Ca++ Transporting, Cardiac Muscle, Slow Twitch 2 (ATP2A2, Accession NM\_001681). Accordingly, utilities of

VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP2A2. KIAA1643 (Accession XM\_035371) is another VGAM629 host target gene. KIAA1643 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1643, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1643 BINDING SITE, designated SEQ ID:32237, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26321] Another function of VGAM629 is therefore inhibition of KIAA1643 (Accession XM\_035371). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1643. MGC10999 (Accession NM\_032307) is another VGAM629 host target gene. MGC10999 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC10999, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

MGC10999 BINDING SITE, designated SEQ ID:26089, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26322] Another function of VGAM629 is therefore inhibition of MGC10999 (Accession NM\_032307). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10999. NAF1 (Accession NM\_006058) is another VGAM629 host target gene. NAF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NAF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAF1 BINDING SITE, designated SEQ ID:12702, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26323] Another function of VGAM629 is therefore inhibition of NAF1 (Accession NM\_006058). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAF1. Tight Junction Protein 2 (zona occludens 2) (TJP2, Accession XM\_005446) is another VGAM629 host target gene.

TJP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TJP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TJP2 BINDING SITE, designated SEQ ID:29981, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26324] Another function of VGAM629 is therefore inhibition of Tight Junction Protein 2 (zona occludens 2) (TJP2, Accession XM\_005446). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TJP2. TSPEAR (Accession NM\_144991) is another VGAM629 host target gene. TSPEAR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSPEAR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSPEAR BINDING SITE, designated SEQ ID:29595, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26325] Another function of VGAM629 is therefore inhibition of TSPEAR (Accession NM\_144991). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSPEAR. LOC113730 (Accession XM\_054631) is another VGAM629 host target gene. LOC113730 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC113730, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC113730 BINDING SITE, designated SEQ ID:36182, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26326] Another function of VGAM629 is therefore inhibition of LOC113730 (Accession XM\_054631). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC113730. LOC152687 (Accession XM\_087503) is another VGAM629 host target gene. LOC152687 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC152687, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152687 BINDING SITE, designated SEQ ID:39302, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26327] Another function of VGAM629 is therefore inhibition of LOC152687 (Accession XM\_087503). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152687. LOC164582 (Accession XM\_092881) is another VGAM629 host target gene. LOC164582 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC164582, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164582 BINDING SITE, designated SEQ ID:40156, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26328] Another function of VGAM629 is therefore inhibition of LOC164582 (Accession XM\_092881). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC164582. LOC220370 (Accession XM\_166943) is another VGAM629 host target gene. LOC220370 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220370, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220370 BINDING SITE, designated SEQ ID:44597, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26329] Another function of VGAM629 is therefore inhibition of LOC220370 (Accession XM\_166943). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220370. LOC221763 (Accession XM\_168107) is another VGAM629 host target gene. LOC221763 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221763, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221763 BINDING SITE, designated SEQ ID:45034, to the nucleotide sequence of VGAM629 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3340.

[26330] Another function of VGAM629 is therefore inhibition of LOC221763 (Accession XM\_168107). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221763. LOC89932 (Accession XM\_027341) is another VGAM629 host target gene. LOC89932 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC89932, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC89932 BINDING SITE, designated SEQ ID:30486, to the nucleotide sequence of VGAM629 RNA, herein designated VGAM RNA, also designated SEQ ID:3340.

[26331] Another function of VGAM629 is therefore inhibition of LOC89932 (Accession XM\_027341). Accordingly, utilities of VGAM629 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC89932. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 630 (VGAM630) viral gene, which modu-



lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26332] VGAM630 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM630 was detected is described hereinabove with reference to Figs. 1–8.

[26333] VGAM630 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Hepatitis GB Virus C. VGAM630 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26334] VGAM630 gene encodes a VGAM630 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM630 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM630 precursor RNA is designated SEQ ID:616, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:616 is located at position 4257 relative to the genome of Hepatitis GB Virus C.

[26335] VGAM630 precursor RNA folds onto itself, forming

VGAM630 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26336] An enzyme complex designated DICER COMPLEX, `dices` the VGAM630 folded precursor RNA into VGAM630 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM630 RNA is designated SEQ ID:3341, and is provided hereinbelow with reference to the sequence listing part.

[26337] VGAM630 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM630 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM630 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26338] VGAM630 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM630 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM630 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM630 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM630 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26339] The complementary binding of VGAM630 RNA, herein designated VGAM RNA, to host target binding sites on VGAM630 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM630 host target RNA into VGAM630 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26340] It is appreciated that VGAM630 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM630 host target genes. The mRNA of each one of this plurality of VGAM630 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM630 RNA, herein designated VGAM RNA, and which when bound by VGAM630 RNA causes inhibition of translation of respective one or more VGAM630 host target proteins.

[26341] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM630 gene, herein designated VGAM GENE, on one or more VGAM630 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26342] It is yet further appreciated that a function of VGAM630 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM630 include diagnosis, prevention and treatment of viral infection by Hepatitis GB Virus C. Specific functions, and accordingly utilities, of VGAM630 correlate with, and may be deduced from, the identity of the host target genes which VGAM630 binds and inhibits, and

the function of these host target genes, as elaborated hereinbelow.

[26343] Nucleotide sequences of the VGAM630 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM630 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM630 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM630 are further described hereinbelow with reference to Table 1.

[26344] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM630 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM630 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26345] As mentioned hereinabove with reference to Fig. 1, a function of VGAM630 gene, herein designated VGAM is inhibition of expression of VGAM630 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM630 correlate with, and may be deduced from, the identity of the target genes which VGAM630 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[26346] Golgi Reassembly Stacking Protein 1, 65kDa (GORASP1, Accession NM\_031899) is a VGAM630 host target gene. GORASP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GORASP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GORASP1 BINDING SITE, designated SEQ ID:25644, to the nucleotide sequence of VGAM630 RNA, herein designated VGAM RNA, also designated SEQ ID:3341.

[26347] A function of VGAM630 is therefore inhibition of Golgi Reassembly Stacking Protein 1, 65kDa (GORASP1, Accession NM\_031899), a gene which has some function with the Golgi apparatus. Accordingly, utilities of VGAM630 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GORASP1. The function of GORASP1 has been established by previous studies. Barr et al. (1998) determined that GOLPH5 interacts with GM130 (OMIM Ref. No. 602580), a Golgi matrix protein, in detergent extracts of rat liver Golgi membranes. They further determined that this complex can bind to the vesicle

docking protein p115 (OMIM Ref. No. 603344). Using in vitro translation and site-directed mutagenesis in conjunction with immunoprecipitation, Barr et al. (1998) localized the critical interacting domains to the C terminus of GM130 and the PDZ-like domain of GOLPH5. Interaction was also found to be critical for the correct targeting of both proteins to the Golgi apparatus. Sutterlin et al. (2002) found that addition of an antibody to the Golgi-associated protein GRASP65 inhibited Golgi fragmentation by mitotic cytosol in permeabilized cells. Microinjecting this antibody or a C-terminal fragment of GRASP65 containing the antibody-binding site into normal rat kidney cells prevented entry into mitosis. Under these conditions the cells had completed S phase but were not in the prophase stage of mitosis. Fragmentation of the Golgi apparatus by nocodazole or brefeldin A treatment prior to or after microinjection of the anti-GRASP65 antibody alleviated the block in mitotic entry. These data suggested that pericentriolar Golgi organization is a sensor for controlling entry into mitosis in mammalian cells.

[26348] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:



- [26349] Barr, F. A.; Nakamura, N.; Warren, G. : Mapping the interaction between GRASP65 and GM130, components of a protein complex involved in the stacking of Golgi cisternae. EMBO J. 17: 3258–3268, 1998. ; and
- [26350] Sutterlin, C.; Hsu, P.; Mallabiabarrena, A.; Malhotra, V. : Fragmentation and dispersal of the pericentriolar Golgi complex is required for entry into mitosis in mammalian cells. Cell 1.
- [26351] Further studies establishing the function and utilities of GORASP1 are found in John Hopkins OMIM database record ID 606867, and in cited publications numbered 9039–5584 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. TATA Box Binding Protein (TBP)–associated Factor, RNA Polymerase I, C, 110kDa (TAF1C, Accession NM\_005679) is another VGAM630 host target gene. TAF1C BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TAF1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAF1C BINDING SITE, designated SEQ ID:12234, to the nucleotide sequence of VGAM630 RNA, herein designated VGAM RNA, also desig–

nated SEQ ID:3341.

[26352] Another function of VGAM630 is therefore inhibition of TATA Box Binding Protein (TBP)–associated Factor, RNA Polymerase I, C, 110kDa (TAF1C, Accession NM\_005679), a gene which belongs to component of the RNA polymerase I and II SL1 transcription factor. Accordingly, utilities of VGAM630 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAF1C. The function of TAF1C and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM191.DRIL2 (Accession NM\_006465) is another VGAM630 host target gene. DRIL2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DRIL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRIL2 BINDING SITE, designated SEQ ID:13181, to the nucleotide sequence of VGAM630 RNA, herein designated VGAM RNA, also designated SEQ ID:3341.

[26353] Another function of VGAM630 is therefore inhibition of DRIL2 (Accession NM\_006465). Accordingly, utilities of

VGAM630 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRIL2.

LOC120114 (Accession XM\_061871) is another VGAM630 host target gene. LOC120114 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120114 BINDING SITE, designated SEQ ID:37212, to the nucleotide sequence of VGAM630 RNA, herein designated VGAM RNA, also designated SEQ ID:3341.

[26354] Another function of VGAM630 is therefore inhibition of LOC120114 (Accession XM\_061871). Accordingly, utilities of VGAM630 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120114. LOC204823 (Accession XM\_115621) is another VGAM630 host target gene. LOC204823 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC204823, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC204823 BINDING SITE, designated SEQ ID:43101, to the nucleotide sequence of VGAM630 RNA, herein designated VGAM RNA, also designated SEQ ID:3341.

[26355] Another function of VGAM630 is therefore inhibition of LOC204823 (Accession XM\_115621). Accordingly, utilities of VGAM630 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC204823. LOC220672 (Accession XM\_017177) is another VGAM630 host target gene. LOC220672 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220672, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220672 BINDING SITE, designated SEQ ID:30307, to the nucleotide sequence of VGAM630 RNA, herein designated VGAM RNA, also designated SEQ ID:3341.

[26356] Another function of VGAM630 is therefore inhibition of LOC220672 (Accession XM\_017177). Accordingly, utilities of VGAM630 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220672. LOC90841 (Accession XM\_034427) is another VGAM630 host target gene. LOC90841 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90841, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90841 BINDING SITE, designated SEQ ID:32109, to the nucleotide sequence of VGAM630 RNA, herein designated VGAM RNA, also designated SEQ ID:3341.

[26357] Another function of VGAM630 is therefore inhibition of LOC90841 (Accession XM\_034427). Accordingly, utilities of VGAM630 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90841. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 631 (VGAM631) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26358] VGAM631 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM631 was detected is described hereinabove with reference to Figs. 1-8.

[26359] VGAM631 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ovine Astrovirus.

VGAM631 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26360] VGAM631 gene encodes a VGAM631 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM631 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM631 precursor RNA is designated SEQ ID:617, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:617 is located at position 1595 relative to the genome of Ovine Astrovirus.

[26361] VGAM631 precursor RNA folds onto itself, forming VGAM631 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[26362] An enzyme complex designated DICER COMPLEX, `dices` the VGAM631 folded precursor RNA into VGAM631 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM631 RNA is designated SEQ ID:3342, and is provided hereinbelow with reference to the sequence listing part.

[26363] VGAM631 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM631 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM631 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26364] VGAM631 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM631 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM631 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM631 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM631 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26365] The complementary binding of VGAM631 RNA, herein designated VGAM RNA, to host target binding sites on VGAM631 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and



BINDING SITE III, inhibits translation of VGAM631 host target RNA into VGAM631 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26366] It is appreciated that VGAM631 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM631 host target genes. The mRNA of each one of this plurality of VGAM631 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM631 RNA, herein designated VGAM RNA, and which when bound by VGAM631 RNA causes inhibition of translation of respective one or more VGAM631 host target proteins.

[26367] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM631 gene, herein designated VGAM GENE, on one or more VGAM631 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26368] It is yet further appreciated that a function of VGAM631 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of viral infection by Ovine Astrovirus. Specific functions, and accordingly utilities, of VGAM631 correlate with, and may be deduced from, the identity of the host target genes which VGAM631 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26369] Nucleotide sequences of the VGAM631 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM631 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM631 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM631 are further described hereinbelow with reference to Table 1.

[26370] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM631 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM631 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26371] As mentioned hereinabove with reference to Fig. 1, a function of VGAM631 gene, herein designated VGAM is inhibition of expression of VGAM631 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM631 correlate with, and may be deduced from, the identity of the target genes which VGAM631 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26372] Deoxyribonuclease I (DNASE1, Accession NM\_005223) is a VGAM631 host target gene. DNASE1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DNASE1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of DNASE1 BINDING SITE, designated SEQ ID:11714, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26373] A function of VGAM631 is therefore inhibition of Deoxyribonuclease I (DNASE1, Accession NM\_005223), a gene which seems to be involved in cell death. Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNASE1. The function of DNASE1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM492. Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051) is another VGAM631 host target gene. EGLN1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EGLN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGLN1 BINDING SITE, designated SEQ ID:22582, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26374] Another function of VGAM631 is therefore inhibition of Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051), a gene which is expressed in the cytoplasm of arterial smooth muscle cells. Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN1. The function of EGLN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM216. Interferon (alpha, beta and omega) Receptor 2 (IFNAR2, Accession NM\_000874) is another VGAM631 host target gene. IFNAR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IFNAR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IFNAR2 BINDING SITE, designated SEQ ID:6552, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26375] Another function of VGAM631 is therefore inhibition of Interferon (alpha, beta and omega) Receptor 2 (IFNAR2, Accession NM\_000874), a gene which is a receptor for in-

terferons alpha and beta. Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IFNAR2. The function of IFNAR2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM487. Collagen, Type XII, Alpha 1 (COL12A1, Accession NM\_080645) is another VGAM631 host target gene. COL12A1 BINDING SITE1 and COL12A1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by COL12A1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COL12A1 BINDING SITE1 and COL12A1 BINDING SITE2, designated SEQ ID:27936 and SEQ ID:10589 respectively, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26376] Another function of VGAM631 is therefore inhibition of Collagen, Type XII, Alpha 1 (COL12A1, Accession NM\_080645). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COL12A1. KIAA1091

(Accession XM\_045750) is another VGAM631 host target gene. KIAA1091 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1091, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1091 BINDING SITE, designated SEQ ID:34543, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26377] Another function of VGAM631 is therefore inhibition of KIAA1091 (Accession XM\_045750). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1091. NRF (Accession NM\_017544) is another VGAM631 host target gene. NRF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRF BINDING SITE, designated SEQ ID:18986, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3342.

[26378] Another function of VGAM631 is therefore inhibition of NRF (Accession NM\_017544). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRF.

LOC148089 (Accession XM\_086040) is another VGAM631 host target gene. LOC148089 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148089, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148089 BINDING SITE, designated SEQ ID:38451, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26379] Another function of VGAM631 is therefore inhibition of LOC148089 (Accession XM\_086040). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148089. LOC148490 (Accession XM\_086210) is another VGAM631 host target gene. LOC148490 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148490, cor-



responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148490 BINDING SITE, designated SEQ ID:38546, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26380] Another function of VGAM631 is therefore inhibition of LOC148490 (Accession XM\_086210). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148490. LOC148764 (Accession XM\_086307) is another VGAM631 host target gene. LOC148764 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148764, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148764 BINDING SITE, designated SEQ ID:38589, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26381] Another function of VGAM631 is therefore inhibition of LOC148764 (Accession XM\_086307). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC148764. LOC155179 (Accession XM\_088169) is another VGAM631 host target gene. LOC155179 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC155179, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155179 BINDING SITE, designated SEQ ID:39552, to the nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26382] Another function of VGAM631 is therefore inhibition of LOC155179 (Accession XM\_088169). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155179. LOC91355 (Accession XM\_037825) is another VGAM631 host target gene. LOC91355 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91355, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91355 BINDING SITE, designated SEQ ID:32702, to the

nucleotide sequence of VGAM631 RNA, herein designated VGAM RNA, also designated SEQ ID:3342.

[26383] Another function of VGAM631 is therefore inhibition of LOC91355 (Accession XM\_037825). Accordingly, utilities of VGAM631 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91355. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 632 (VGAM632) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26384] VGAM632 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM632 was detected is described hereinabove with reference to Figs. 1–8.

[26385] VGAM632 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ovine Astrovirus. VGAM632 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26386] VGAM632 gene encodes a VGAM632 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM632 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM632 precursor RNA is designated SEQ ID:618, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:618 is located at position 1405 relative to the genome of Ovine Astrovirus.

[26387] VGAM632 precursor RNA folds onto itself, forming VGAM632 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26388] An enzyme complex designated DICER COMPLEX, `dices` the VGAM632 folded precursor RNA into VGAM632 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM632 RNA is designated SEQ ID:3343, and is provided hereinbelow with reference to the sequence listing part.

[26389] VGAM632 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM632 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM632 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26390] VGAM632 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM632 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM632 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM632 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM632 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26391] The complementary binding of VGAM632 RNA, herein designated VGAM RNA, to host target binding sites on VGAM632 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM632 host target RNA into VGAM632 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26392] It is appreciated that VGAM632 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM632 host target genes. The mRNA of each one of this plurality of VGAM632 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM632 RNA, herein designated VGAM RNA, and which when bound by VGAM632 RNA causes inhibition of translation of respective one or more VGAM632 host target proteins.

[26393] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM632 gene, herein designated VGAM GENE, on one or more VGAM632 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[26394] It is yet further appreciated that a function of VGAM632 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of viral infection by Ovine Astrovirus. Specific functions, and accordingly utilities, of VGAM632 correlate with, and may be deduced from, the identity of the host target genes which VGAM632 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[26395] Nucleotide sequences of the VGAM632 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM632 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM632 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM632 are further described hereinbelow with reference to Table 1.

[26396] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM632 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM632 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26397] As mentioned hereinabove with reference to Fig. 1, a function of VGAM632 gene, herein designated VGAM is inhibition of expression of VGAM632 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM632 correlate with, and may be deduced from, the identity of the target genes which VGAM632 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26398] Calcium Channel, Voltage-dependent, Gamma Subunit 6 (CACNG6, Accession NM\_031897) is a VGAM632 host target gene. CACNG6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CACNG6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CACNG6 BINDING SITE, designated SEQ ID:25642, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26399] A function of VGAM632 is therefore inhibition of Calcium

Channel, Voltage-dependent, Gamma Subunit 6 (CACNG6, Accession NM\_031897), a gene which plays a role in excitation-contraction coupling. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CACNG6. The function of CACNG6 has been established by previous studies. Voltage-dependent calcium channels couple membrane depolarization in a number of cellular processes. These activities are regulated by distinct channels composed of the pore-forming alpha-1 (e.g., CACNA1D; 114206) subunit and the modulatory beta (e.g., CACNB1; 114207), alpha-2/delta (e.g., CACNA2D1; 114204), and gamma (e.g., CACNG1; 114209) subunits. By RT-PCR and genomic sequence analysis, Burgess et al. (2001) determined that the CACNG6 gene, like CACNG7 and CACNG8, contains 4 exons. A potential splice variant lacking exon 3 would eliminate 2 transmembrane domains.

[26400] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26401] Burgess, D. L.; Gefrides, L. A.; Foreman, P. J.; Noebels, J. L. : A cluster of three novel Ca(2+) channel gamma subunit genes on chromosome 19q13.4: evolution and expression

profile of the gamma subunit gene family. Genomics 71: 339–350, 2001. ; and

[26402] Chu, P.-J.; Robertson, H. M.; Best, P. M. : Calcium channel gamma subunits provide insights into the evolution of this gene family. Gene 280: 37–48, 2001.

[26403] Further studies establishing the function and utilities of CACNG6 are found in John Hopkins OMIM database record ID 606898, and in cited publications numbered 4526–4527 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chimerin (chimaerin) 1 (CHN1, Accession NM\_001822) is another VGAM632 host target gene. CHN1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CHN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHN1 BINDING SITE, designated SEQ ID:7562, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26404] Another function of VGAM632 is therefore inhibition of Chimerin (chimaerin) 1 (CHN1, Accession NM\_001822), a gene which may play an important role in neuronal signal–

transduction mechanisms. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHN1. The function of CHN1 has been established by previous studies. Hall et al. (1990) isolated a novel human brain cDNA sequence encoding n-chimerin, a 34,000 M(r) protein. They found that the N-terminal half shared almost 50% identity with sequences in the regulatory domain of protein kinase C (OMIM Ref. No. 176960); the C-terminal half had 42% identity with the C-terminal region of BCR, the product of the breakpoint cluster region gene involved in the Philadelphia chromosome translocation (OMIM Ref. No. 151410). Also known as alpha-1-chimerin, n-chimerin is a brain GTPase-activating protein (GAP) for the RAS-related p21 (RAC). Hall et al. (1993) found another form of chimerin, termed alpha-2-chimerin, and showed that it is the product of an alternately spliced transcript of the human n-chimerin gene. The mRNAs corresponding to the 2 forms of chimerin were expressed differently. The single human n-chimerin gene was mapped to 2q31-q32.1 by Southern analysis of a hybrid cell DNA panel and by fluorescence in situ hybridization.

[26405] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [26406] Hall, C.; Monfries, C.; Smith, P.; Lim, H. H.; Kozma, R.; Ahmed, S.; Vanniasingham, V.; Leung, T.; Lim, L. : Novel human brain cDNA encoding a 34,000 M(r) protein n-chimaerin, related to both the regulatory domain of protein kinase C and BCR, the product of the breakpoint cluster region gene. J. Molec. Biol. 211: 11-16, 1990. ; and
- [26407] Hall, C.; Sin, W. C.; Teo, M.; Michael, G. J.; Smith, P.; Dong, J. M.; Lim, H. H.; Manser, E.; Spurr, N. K.; Jones, T. A.; Lim, L. : Alpha-2-chimerin, an SH2-containing GTPase-activator.
- [26408] Further studies establishing the function and utilities of CHN1 are found in John Hopkins OMIM database record ID 118423, and in cited publications numbered 3719-3720 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Early Growth Response 3 (EGR3, Accession XM\_005040) is another VGAM632 host target gene. EGR3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of EGR3 BINDING SITE, designated SEQ ID:29955, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26409] Another function of VGAM632 is therefore inhibition of Early Growth Response 3 (EGR3, Accession XM\_005040), a gene which is a putative transcription factor. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGR3. The function of EGR3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM189. Forkhead Box E3 (FOX E3, Accession NM\_012186) is another VGAM632 host target gene. FOX E3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FOX E3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOX E3 BINDING SITE, designated SEQ ID:14472, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26410] Another function of VGAM632 is therefore inhibition of Forkhead Box E3 (FOXE3, Accession NM\_012186), a gene which regulates embryonic development. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOXE3. The function of FOXE3 has been established by previous studies. Dysgenesis of the anterior segment of the eye is frequently associated with cataracts and glaucoma, resulting in visual disability in childhood. Semina et al. (2001) reported a single nucleotide insertion in the coding region of the FOXE3 gene in a family with anterior segment ocular dysgenesis and cataracts (OMIM Ref. No. 107250). The mutation caused a frameshift that resulted in an abnormal sequence of 5 terminal amino acids and an addition of 111 amino acids to the predicted protein. The mutation was present in 2 affected individuals from this family and was not identified in 180 normal control chromosomes. Animal model experiments lend further support to the function of FOXE3. Blixt et al. (2000) hypothesized that mutations in Foxe3 could be responsible for the phenotype observed in dysgenetic lens (dyl) mutant mice. In these mice, the lens vesicle fails to separate from the ectoderm, causing a fusion between the

lens and the cornea. Blixt et al. (2000) identified 2 mutations within the DNA-binding domain of Foxe3 in dyl mice: phe93-to-leu and phe98-to-ser. These 2 phenylalanine residues are highly conserved in all forkhead proteins and Blixt et al. (2000) predicted the mutations would obliterate DNA binding.

[26411] It is appreciated that the abovementioned animal model for FOXE3 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[26412] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26413] Blixt, A.; Mahlapuu, M.; Aitola, M.; Peltö-Huikko, M.; Enerback, S.; Carlsson, P. : A forkhead gene, FoxE3, is essential for lens epithelial proliferation and closure of the lens vesicle. *Genes Dev.* 14: 245–254, 2000. ; and

[26414] Semina, E. V.; Brownell, I.; Mintz-Hittner, H. A.; Murray, J. C.; Jamrich, M. : Mutations in the human forkhead transcription factor FOXE3 associated with anterior segment ocular dysgen.

[26415] Further studies establishing the function and utilities of FOXE3 are found in John Hopkins OMIM database record



ID 601094, and in cited publications numbered 1252 and 12528 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Forkhead Box M1 (FOXM1, Accession NM\_021953) is another VGAM632 host target gene. FOXM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FOXM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOXM1 BINDING SITE, designated SEQ ID:22482, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26416] Another function of VGAM632 is therefore inhibition of Forkhead Box M1 (FOXM1, Accession NM\_021953), a gene which may play a role in the control of cell proliferation. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOXM1. The function of FOXM1 has been established by previous studies. The 'forkhead' gene family, originally identified in *Drosophila*, comprises transcription factors with a conserved 100-amino acid DNA-binding motif. One group of factors with the forkhead, or

winged-helix, domain is the hepatocyte nuclear factor-3 family of proteins, which appears to regulate cell-specific transcription in hepatocytes and in respiratory and intestinal epithelia. In an attempt to identify forkhead domain transcription factors involved in intestinal cell differentiation, Ye et al. (1997) isolated FKHL16, which they designated HNF3/forkhead homolog-11 (HFH11), from a human colon carcinoma cell line. On Northern blots, FKHL16 is expressed primarily in thymus, testis, small intestine, and colon, moderately in ovary, and at reduced levels in other tissues. Ye et al. (1997) found 2 alternatively spliced FKHL16 mRNAs, yielding predicted proteins of 801 (OMIM Ref. No. HFH11A) and 748 (OMIM Ref. No. HFH11B) amino acids. Both isoforms contain 2 PEST regions, associated with rapid protein degradation. Expression studies in mouse revealed that Fkhl16 is transcribed broadly in embryos, but is expressed only in adult organs containing proliferating cells involved in replenishing differentiated cell populations or in response to growth factors released during injury or repair. By analyzing the promoter region of human FKHL16, or TRIDENT, Korver et al. (1997) found that the 300 bp upstream of the transcription start site are essential for the cell cycle-specific expression of

FKHL16. They stated that the promoter data in combination with the expression of FKHL16 in cycling, but not resting, cells indicate that this protein is likely to play a role in the control of cell proliferation. By analysis of cDNA microarrays, Ly et al. (2000) showed that diminished proliferation exhibited by fibroblasts from either elderly patients or patients with Hutchinson–Gilford progeria (OMIM Ref. No. 176670) was associated with reduced expression of cell cycle genes as well as a decline in FOXM1B (OMIM Ref. No. HFH11B) levels. Wang et al. (2001) showed that increased levels of Foxm1b in regenerating liver of old transgenic mice restored the sharp peaks in hepatocyte DNA replication and mitosis that are the hallmarks of young regenerating mouse liver. Restoration of the young regenerating liver phenotype was associated with increased expression of numerous cell cycle regulatory genes. Cotransfection assays in the human hepatoma HepG2 cell line demonstrated that FOXM1B protein stimulated expression of both the cyclin B1 (OMIM Ref. No. 123836) and cyclin D1 (OMIM Ref. No. 168461) promoters, suggesting that these cyclin genes are a direct FOXM1B transcription target. The results suggested that FOXM1B controls the transcription network of genes that

are essential for cell division and exit from mitosis. The results indicated that reduced expression of the FOXM1B transcription factor contributes to the decline in cellular proliferation observed in the aging process.

[26417] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26418] Westendorf, J. M.; Rao, P. N.; Gerace, L. : Cloning of cDNAs for M-phase phosphoproteins recognized by the MPM2 monoclonal antibody and determination of the phosphorylated epitope. Proc. Nat. Acad. Sci. 91: 714–718, 1994. ; and

[26419] Yao, K.–M.; Sha, M.; Lu, Z.; Wong, G. G. : Molecular analysis of a novel winged helix protein, WIN: expression pattern, DNA binding property, and alternative splicing within the DNA bin.

[26420] Further studies establishing the function and utilities of FOXM1 are found in John Hopkins OMIM database record ID 602341, and in cited publications numbered 6306–630 and 6311 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Galanin (GAL, Accession XM\_166189) is another VGAM632 host target gene. GAL BINDING SITE is HOST TARGET binding

site found in the 5' untranslated region of mRNA encoded by GAL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAL BINDING SITE, designated SEQ ID:43999, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26421] Another function of VGAM632 is therefore inhibition of Galanin (GAL, Accession XM\_166189), a gene which stimulates LH secretion and enhances LHRH-induced LH release from dispersed anterior pituitary cells in vitro. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAL. The function of GAL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM514. Potassium Channel, Subfamily K, Member 7 (KCNK7, Accession NM\_033456) is another VGAM632 host target gene. KCNK7 BINDING SITE1 through KCNK7 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KCNK7, corresponding to HOST TARGET binding sites

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNK7 BINDING SITE1 through KCNK7 BINDING SITE4, designated SEQ ID:27254, SEQ ID:27199, SEQ ID:27200 and SEQ ID:12268 respectively, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26422] Another function of VGAM632 is therefore inhibition of Potassium Channel, Subfamily K, Member 7 (KCNK7, Accession NM\_033456). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNK7. Mannosyl (alpha-1,3-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT1, Accession NM\_002406) is another VGAM632 host target gene. MGAT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGAT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAT1 BINDING SITE, designated SEQ ID:8226, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ

ID:3343.

[26423] Another function of VGAM632 is therefore inhibition of Mannosyl (alpha-1,3-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT1, Accession NM\_002406), a gene which exists as a single protein-encoding exon. Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGAT1. The function of MGAT1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM165. Oculocerebrorenal Syndrome of Lowe (OCRL, Accession NM\_000276) is another VGAM632 host target gene. OCRL BINDING SITE1 and OCRL BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by OCRL, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OCRL BINDING SITE1 and OCRL BINDING SITE2, designated SEQ ID:5818 and SEQ ID:7305 respectively, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26424] Another function of VGAM632 is therefore inhibition of Oculocerebrorenal Syndrome of Lowe (OCRL, Accession NM\_000276). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OCRL. Src-like-adaptor 2 (SLA2, Accession NM\_032214) is another VGAM632 host target gene. SLA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLA2 BINDING SITE, designated SEQ ID:25943, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26425] Another function of VGAM632 is therefore inhibition of Src-like-adaptor 2 (SLA2, Accession NM\_032214). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLA2. Chromosome 11 Open Reading Frame 11 (C11orf11, Accession XM\_167769) is another VGAM632 host target gene. C11orf11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by C11orf11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C11orf11 BINDING SITE, designated SEQ ID:44789, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26426] Another function of VGAM632 is therefore inhibition of Chromosome 11 Open Reading Frame 11 (C11orf11, Accession XM\_167769). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C11orf11. CGI-203 (Accession NM\_020408) is another VGAM632 host target gene. CGI-203 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CGI-203, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CGI-203 BINDING SITE, designated SEQ ID:21675, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26427] Another function of VGAM632 is therefore inhibition of

CGI-203 (Accession NM\_020408). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CGI-203. KIAA0222 (Accession NM\_014643) is another VGAM632 host target gene. KIAA0222 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0222, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0222 BINDING SITE, designated SEQ ID:16046, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26428] Another function of VGAM632 is therefore inhibition of KIAA0222 (Accession NM\_014643). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0222. KIAA1915 (Accession XM\_055481) is another VGAM632 host target gene. KIAA1915 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1915, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1915 BINDING SITE, designated SEQ ID:36274, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26429] Another function of VGAM632 is therefore inhibition of KIAA1915 (Accession XM\_055481). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1915. Quiescin Q6 (QSCN6, Accession NM\_002826) is another VGAM632 host target gene. QSCN6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by QSCN6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of QSCN6 BINDING SITE, designated SEQ ID:8698, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26430] Another function of VGAM632 is therefore inhibition of Quiescin Q6 (QSCN6, Accession NM\_002826). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with QSCN6. UCK1 (Accession NM\_031432) is an-

other VGAM632 host target gene. UCK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UCK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UCK1 BINDING SITE, designated SEQ ID:25429, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26431] Another function of VGAM632 is therefore inhibition of UCK1 (Accession NM\_031432). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UCK1. LOC149134 (Accession XM\_097594) is another VGAM632 host target gene. LOC149134 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149134, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149134 BINDING SITE, designated SEQ ID:40960, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26432] Another function of VGAM632 is therefore inhibition of LOC149134 (Accession XM\_097594). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149134. LOC149837 (Accession XM\_097747) is another VGAM632 host target gene. LOC149837 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149837, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149837 BINDING SITE, designated SEQ ID:41103, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26433] Another function of VGAM632 is therefore inhibition of LOC149837 (Accession XM\_097747). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149837. LOC151723 (Accession XM\_093395) is another VGAM632 host target gene. LOC151723 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151723, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151723 BINDING SITE, designated SEQ ID:40192, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26434] Another function of VGAM632 is therefore inhibition of LOC151723 (Accession XM\_093395). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151723. LOC157653 (Accession XM\_088353) is another VGAM632 host target gene. LOC157653 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157653, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157653 BINDING SITE, designated SEQ ID:39636, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26435] Another function of VGAM632 is therefore inhibition of LOC157653 (Accession XM\_088353). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC157653. LOC255397 (Accession XM\_173868) is another VGAM632 host target gene. LOC255397 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255397 BINDING SITE, designated SEQ ID:46566, to the nucleotide sequence of VGAM632 RNA, herein designated VGAM RNA, also designated SEQ ID:3343.

[26436] Another function of VGAM632 is therefore inhibition of LOC255397 (Accession XM\_173868). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255397. LOC58525 (Accession XM\_086045) is another VGAM632 host target gene. LOC58525 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC58525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC58525 BINDING SITE, designated SEQ ID:38458, to the nucleotide sequence of VGAM632 RNA, herein designated

VGAM RNA, also designated SEQ ID:3343.

[26437] Another function of VGAM632 is therefore inhibition of LOC58525 (Accession XM\_086045). Accordingly, utilities of VGAM632 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC58525. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 633 (VGAM633) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26438] VGAM633 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM633 was detected is described hereinabove with reference to Figs. 1–8.

[26439] VGAM633 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turkey Astrovirus. VGAM633 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26440] VGAM633 gene encodes a VGAM633 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other



miRNA genes, and unlike most ordinary genes, VGAM633 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM633 precursor RNA is designated SEQ ID:619, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:619 is located at position 2114 relative to the genome of Turkey Astrovirus.

[26441] VGAM633 precursor RNA folds onto itself, forming VGAM633 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26442] An enzyme complex designated DICER COMPLEX, `dices` the VGAM633 folded precursor RNA into VGAM633 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM633 RNA is designated SEQ ID:3344, and is provided hereinbelow with reference to the sequence listing part.

[26443] VGAM633 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM633 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM633 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[26444] VGAM633 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM633 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM633 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM633 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM633 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[26445] The complementary binding of VGAM633 RNA, herein designated VGAM RNA, to host target binding sites on VGAM633 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM633 host target RNA into VGAM633 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26446] It is appreciated that VGAM633 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM633 host target genes. The mRNA of

each one of this plurality of VGAM633 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM633 RNA, herein designated VGAM RNA, and which when bound by VGAM633 RNA causes inhibition of translation of respective one or more VGAM633 host target proteins.

[26447] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM633 gene, herein designated VGAM GENE, on one or more VGAM633 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[26448] It is yet further appreciated that a function of VGAM633 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of viral infection by Turkey Astrovirus. Specific functions, and accordingly utilities, of VGAM633 correlate with, and may be deduced from, the identity of the host target genes which VGAM633 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26449] Nucleotide sequences of the VGAM633 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM633 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM633 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM633 are further described hereinbelow with reference to Table 1.

[26450] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM633 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM633 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[26451] As mentioned hereinabove with reference to Fig. 1, a function of VGAM633 gene, herein designated VGAM is inhibition of expression of VGAM633 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM633 correlate with, and may be deduced from, the identity of the target genes which VGAM633 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26452] Fibroblast Growth Factor 5 (FGF5, Accession NM\_033143) is a VGAM633 host target gene. FGF5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FGF5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF5 BINDING SITE, designated SEQ ID:26995, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26453] A function of VGAM633 is therefore inhibition of Fibroblast Growth Factor 5 (FGF5, Accession NM\_033143), a gene which induces transformation and may regulate neu-

ronal differentiation. Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF5. The function of FGF5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM276.Huntingtin Interacting Protein 1 (HIP1, Accession NM\_005338) is another VGAM633 host target gene. HIP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HIP1 BINDING SITE, designated SEQ ID:11809, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26454] Another function of VGAM633 is therefore inhibition of Huntingtin Interacting Protein 1 (HIP1, Accession NM\_005338), a gene which is a membrane protein and interacts with huntingtin. Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HIP1. The function of HIP1 and its association with various diseases and clini-

cal conditions, has been established by previous studies, as described hereinabove with reference to VGAM474. Transforming Growth Factor, Beta Receptor III (betaglycan, 300kDa) (TGFB3, Accession NM\_003243) is another VGAM633 host target gene. TGFB3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TGFB3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TGFB3 BINDING SITE, designated SEQ ID:9246, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26455] Another function of VGAM633 is therefore inhibition of Transforming Growth Factor, Beta Receptor III (betaglycan, 300kDa) (TGFB3, Accession NM\_003243), a gene which involves in capturing and retaining TGF-beta for presentation to the signaling receptors. Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TGFB3. The function of TGFB3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference



to VGAM139.FLJ20413 (Accession NM\_017808) is another VGAM633 host target gene. FLJ20413 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20413, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20413 BINDING SITE, designated SEQ ID:19449, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26456] Another function of VGAM633 is therefore inhibition of FLJ20413 (Accession NM\_017808). Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20413. Heat Shock 90kDa Protein 1, Alpha-like 3 (HSPCAL3, Accession XM\_084514) is another VGAM633 host target gene. HSPCAL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPCAL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPCAL3 BINDING SITE, designated SEQ ID:37616, to the nucleotide sequence of VGAM633 RNA,

herein designated VGAM RNA, also designated SEQ ID:3344.

[26457] Another function of VGAM633 is therefore inhibition of Heat Shock 90kDa Protein 1, Alpha-like 3 (HSPCAL3, Accession XM\_084514). Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPCAL3.

KIAA0608 (Accession XM\_051081) is another VGAM633 host target gene. KIAA0608 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0608, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0608 BINDING SITE, designated SEQ ID:35735, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26458] Another function of VGAM633 is therefore inhibition of KIAA0608 (Accession XM\_051081). Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0608. KIAA1026 (Accession XM\_048825) is another VGAM633 host target gene. KIAA1026 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1026, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1026 BINDING SITE, designated SEQ ID:35272, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26459] Another function of VGAM633 is therefore inhibition of KIAA1026 (Accession XM\_048825). Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1026. LOC220549 (Accession XM\_167521) is another VGAM633 host target gene. LOC220549 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220549, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220549 BINDING SITE, designated SEQ ID:44653, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26460] Another function of VGAM633 is therefore inhibition of

LOC220549 (Accession XM\_167521). Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220549. LOC51696 (Accession NM\_016217) is another VGAM633 host target gene. LOC51696 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51696 BINDING SITE, designated SEQ ID:18306, to the nucleotide sequence of VGAM633 RNA, herein designated VGAM RNA, also designated SEQ ID:3344.

[26461] Another function of VGAM633 is therefore inhibition of LOC51696 (Accession NM\_016217). Accordingly, utilities of VGAM633 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51696. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 634 (VGAM634) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[26462] VGAM634 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM634 was detected is described hereinabove with reference to Figs. 1–8.

[26463] VGAM634 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turkey Astrovirus. VGAM634 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26464] VGAM634 gene encodes a VGAM634 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM634 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM634 precursor RNA is designated SEQ ID:620, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:620 is located at position 1689 relative to the genome of Turkey Astrovirus.

[26465] VGAM634 precursor RNA folds onto itself, forming VGAM634 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[26466] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM634 folded precursor RNA into VGAM634 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 44%) nucleotide se-  
quence of VGAM634 RNA is designated SEQ ID:3345, and  
is provided hereinbelow with reference to the sequence  
listing part.

[26467] VGAM634 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM634 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM634 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[26468] VGAM634 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM634 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM634 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM634 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM634 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[26469] The complementary binding of VGAM634 RNA, herein designated VGAM RNA, to host target binding sites on VGAM634 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM634 host target RNA into VGAM634 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26470] It is appreciated that VGAM634 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM634 host target genes. The mRNA of each one of this plurality of VGAM634 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM634 RNA, herein designated VGAM RNA, and which when bound by VGAM634 RNA causes inhibition of translation of respective one or more VGAM634 host target proteins.

[26471] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM634 gene, herein designated VGAM GENE, on one or



more VGAM634 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26472] It is yet further appreciated that a function of VGAM634 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of viral infection by Turkey Astrovirus. Specific functions, and accordingly utilities, of VGAM634 correlate with, and may be deduced from, the identity of the host target genes which VGAM634 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [26473] Nucleotide sequences of the VGAM634 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM634 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM634 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM634 are further described hereinbelow with reference to Table 1.
- [26474] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM634 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM634 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [26475] As mentioned hereinabove with reference to Fig. 1, a function of VGAM634 gene, herein designated VGAM is inhibition of expression of VGAM634 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM634 correlate with, and may be deduced from, the identity of the target genes which VGAM634 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [26476] Chondroitin Sulfate Proteoglycan 3 (neurocan) (CSPG3,

Accession NM\_004386) is a VGAM634 host target gene. CSPG3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSPG3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSPG3 BINDING SITE, designated SEQ ID:10614, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26477] A function of VGAM634 is therefore inhibition of Chondroitin Sulfate Proteoglycan 3 (neurocan) (CSPG3, Accession NM\_004386), a gene which may play a role in modulating cell adhesion and migration. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSPG3. The function of CSPG3 has been established by previous studies. Neurocan was first described in the early postnatal rat brain where it accounts for 20 to 30% of the total chondroitin sulfate proteoglycan. Rauch et al. (1992) cloned the rat cDNA using degenerate primers based on partial amino acid sequence of immunoaffinity-purified protein. The mouse neurocan cDNA encodes a deduced

1,257-amino acid protein with a predicted molecular mass of 136 kD. The large protein is processed into a smaller form in the adult brain. The predicted protein has a 22-amino acid signal peptide followed by an immunoglobulin-like domain and repeating motifs characteristic of the hyaluronic acid-binding region of aggregating proteoglycans. The C terminus shows approximately 60% identity to the fibroblast and cartilage proteoglycans versican (OMIM Ref. No. 118661) and aggrecan (OMIM Ref. No. 155760). Northern blots detected a 7.5-kb transcript from 4-day and adult rat brains Prange et al. (1998) cloned human neurocan cDNAs from infant and adult brain cDNA libraries. The deduced 1,321-amino acid protein shares 63% sequence identity with both mouse and rat neurocan proteins. Like other known proteoglycans, its N terminus contains an immunoglobulin domain and a series of hyaluronic acid-binding tandem repeats, and its C terminus contains an EGF-like domain, a lectin-like domain, and a complement regulatory-like domain. Northern blot analysis detected expression of a 7.5-kb transcript in fetal and adult tissues from all brain regions tested

[26478] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

[26479] Rauch, U.; Grimpe, B.; Kulbe, G.; Arnold–Ammer, I.; Beier, D. R.; Fassler, R. : Structure and chromosomal localization of the mouse neurocan gene. Genomics 28: 405–410, 1995. ; and

[26480] Prange, C. K.; Pennacchio, L. A.; Lieuallen, K.; Fan, W.; Lennon, G. G. : Characterization of the human neurocan gene, CSPG3. Gene 221: 199–205, 1998.

[26481] Further studies establishing the function and utilities of CSPG3 are found in John Hopkins OMIM database record ID 600826, and in cited publications numbered 7779–7782 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Dishevelled Associated Activator of Morphogenesis 2 (DAAM2, Accession XM\_166434) is another VGAM634 host target gene. DAAM2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DAAM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAAM2 BINDING SITE, designated SEQ ID:44336, to the nucleotide sequence of

VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26482] Another function of VGAM634 is therefore inhibition of Dishevelled Associated Activator of Morphogenesis 2 (DAAM2, Accession XM\_166434), a gene which controls cell polarity and movement during development. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAAM2. The function of DAAM2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. Estrogen-related Receptor Beta Like 1 (ESRRBL1, Accession NM\_018010) is another VGAM634 host target gene. ESRRBL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESRRBL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRBL1 BINDING SITE, designated SEQ ID:19741, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26483] Another function of VGAM634 is therefore inhibition of

Estrogen-related Receptor Beta Like 1 (ESRRBL1, Accession NM\_018010). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESRRBL1. Growth Factor Receptor-bound Protein 10 (GRB10, Accession NM\_005311) is another VGAM634 host target gene. GRB10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRB10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRB10 BINDING SITE, designated SEQ ID:11788, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26484] Another function of VGAM634 is therefore inhibition of Growth Factor Receptor-bound Protein 10 (GRB10, Accession NM\_005311), a gene which plays a functional role in insulin and IGF-I signaling. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRB10. The function of GRB10 and its association with various diseases and clinical conditions, has been established by

previous studies, as described hereinabove with reference to VGAM441. Interleukin 1, Alpha (IL1A, Accession XM\_031221) is another VGAM634 host target gene. IL1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL1A BINDING SITE, designated SEQ ID:31308, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26485] Another function of VGAM634 is therefore inhibition of Interleukin 1, Alpha (IL1A, Accession XM\_031221), a gene which stimulates thymocyte proliferation by inducing il-2 release, b-cell maturation & proliferation, & fibroblast growth factor activity. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL1A. The function of IL1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM475. IRTA1 (Accession NM\_031282) is another VGAM634 host target gene. IRTA1 BINDING SITE is HOST



TARGET binding site found in the 3' untranslated region of mRNA encoded by IRTA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IRTA1 BINDING SITE, designated SEQ ID:25303, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26486] Another function of VGAM634 is therefore inhibition of IRTA1 (Accession NM\_031282). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IRTA1. Arginine-glutamic Acid Dipeptide (RE) Repeats (RERE, Accession NM\_012102) is another VGAM634 host target gene. RERE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RERE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RERE BINDING SITE, designated SEQ ID:14411, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26487] Another function of VGAM634 is therefore inhibition of

Arginine–glutamic Acid Dipeptide (RE) Repeats (RERE, Accession NM\_012102), a gene which binds DRPLA and locates in the nucleus. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RERE. The function of RERE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM51.RNA (guanine–7–) Methyltransferase (RNMT, Accession NM\_003799) is another VGAM634 host target gene. RNMT BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RNMT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNMT BINDING SITE, designated SEQ ID:9892, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26488] Another function of VGAM634 is therefore inhibition of RNA (guanine–7–) Methyltransferase (RNMT, Accession NM\_003799), a gene which catalyzes the methylation of GpppN– at the guanine N7 position. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with RNMT. The function of RNMT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178.RU2 (Accession NM\_016356) is another VGAM634 host target gene. RU2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RU2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RU2 BINDING SITE, designated SEQ ID:18494, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26489] Another function of VGAM634 is therefore inhibition of RU2 (Accession NM\_016356), a gene which expressed ubiquitously, potentially useful antigens for cancer immunotherapy cannot be predicted from the sequence of the normal cellular protein. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RU2. The function of RU2 has been established by previous studies. Tumor antigens recognized by cytolytic T cells (CTLs) can

be classified into 4 groups: shared tumor-specific antigens encoded by MAGE-type genes (e.g., MAGEA1; 300016) that are silent in most normal tissues and expressed in many tumors; differentiation antigens that are also expressed in normal cells; antigens resulting from tumor-specific point mutations; and antigens overexpressed in tumor cells. By screening cells expressing both HLA-B7 and kidney tumor cell RNA with autologous CTLs, followed by PCR, van den Eynde et al. (1999) obtained cDNAs encoding RU2, which is identical to the KIAA1154 gene identified by Hirosawa et al. (1999). Genomic sequence analysis determined that RU2 is transcribed as a 'normal' gene, resulting in a sense transcript (RU2S), and in the opposite direction, resulting in a shorter antisense transcript (RU2AS) found in tumors. Testing of synthetic peptides determined that the tumor antigen binding to HLA-B7 has the sequence LPRWPPPQL. Northern blot analysis revealed that the full-length gene is expressed as a 2.2-kb transcript. RT-PCR analysis detected ubiquitous expression of the full-length RU2S transcript, but expression of the RU2AS transcript was restricted to normal kidney, bladder, liver, and testis, as well as tumors of various histologic origins. The deduced RU2S protein contains

476 amino acids, while the RU2AS protein contains 84 residues. Van den Eynde et al. (1999) concluded that potentially useful antigens for cancer immunotherapy cannot be predicted from the sequence of the normal cellular protein. Using FISH, van den Eynde et al. (1999) mapped the RU2 gene to 6p22.1.

[26490] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26491] Hirosawa, M.; Nagase, T.; Ishikawa, K.; Kikuno, R.; Nomura, N.; Ohara, O. : Characterization of cDNA clones selected by the GeneMark analysis from size-fractionated cDNA libraries from human brain. DNA Res. 6: 329–336, 1999. ; and

[26492] van den Eynde, B. J.; Gaugler, B.; Probst-Kepper, M.; Michaux, L.; Devuyst, O.; Lorge, F.; Weynants, P.; Boon, T. : A new antigen recognized by cytolytic T lymphocytes on a human kidney.

[26493] Further studies establishing the function and utilities of RU2 are found in John Hopkins OMIM database record ID 605755, and in cited publications numbered 7480 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. TRAM (Accession

NM\_014294) is another VGAM634 host target gene. TRAM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRAM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRAM BINDING SITE, designated SEQ ID:15592, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26494] Another function of VGAM634 is therefore inhibition of TRAM (Accession NM\_014294). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRAM. Ubiquitin-conjugating Enzyme E2A (RAD6 homolog) (UBE2A, Accession NM\_003336) is another VGAM634 host target gene. UBE2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2A BINDING SITE, designated SEQ ID:9343, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ

ID:3345.

[26495] Another function of VGAM634 is therefore inhibition of Ubiquitin-conjugating Enzyme E2A (RAD6 homolog) (UBE2A, Accession NM\_003336), a gene which catalyzes the covalent attachment of ubiquitin to other proteins and is required for postreplication repair of uv-damaged dna. Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2A. The function of UBE2A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM294.ADAM-like, Decysin 1 (ADAMDEC1, Accession NM\_014479) is another VGAM634 host target gene. ADAMDEC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAMDEC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAMDEC1 BINDING SITE, designated SEQ ID:15824, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26496] Another function of VGAM634 is therefore inhibition of

ADAM-like, Decysin 1 (ADAMDEC1, Accession NM\_014479). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAMDEC1. APCL (Accession NM\_005883) is another VGAM634 host target gene. APCL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APCL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APCL BINDING SITE, designated SEQ ID:12496, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26497] Another function of VGAM634 is therefore inhibition of APCL (Accession NM\_005883). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APCL. Rho GTPase Activating Protein 8 (ARHGAP8, Accession NM\_017701) is another VGAM634 host target gene. ARHGAP8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ARHGAP8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.



Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP8 BINDING SITE, designated SEQ ID:19274, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26498] Another function of VGAM634 is therefore inhibition of Rho GTPase Activating Protein 8 (ARHGAP8, Accession NM\_017701). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP8. BCAA (Accession NM\_016374) is another VGAM634 host target gene. BCAA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCAA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCAA BINDING SITE, designated SEQ ID:18514, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26499] Another function of VGAM634 is therefore inhibition of BCAA (Accession NM\_016374). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCAA.

CAMP-GEFII (Accession NM\_007023) is another VGAM634 host target gene. CAMP-GEFII BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAMP-GEFII, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAMP-GEFII BINDING SITE, designated SEQ ID:13880, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26500] Another function of VGAM634 is therefore inhibition of CAMP-GEFII (Accession NM\_007023). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAMP-GEFII. Cytoskeleton-associated Protein 4 (CKAP4, Accession NM\_006825) is another VGAM634 host target gene. CKAP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CKAP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CKAP4 BINDING SITE, designated SEQ ID:13703, to the nucleotide sequence of VGAM634 RNA,

herein designated VGAM RNA, also designated SEQ ID:3345.

[26501] Another function of VGAM634 is therefore inhibition of Cytoskeleton-associated Protein 4 (CKAP4, Accession NM\_006825). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CKAP4. DKFZp434E0519 (Accession NM\_032247) is another VGAM634 host target gene. DKFZp434E0519 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp434E0519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434E0519 BINDING SITE, designated SEQ ID:25985, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26502] Another function of VGAM634 is therefore inhibition of DKFZp434E0519 (Accession NM\_032247). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434E0519. FLJ11078 (Accession NM\_018316) is another VGAM634 host target gene. FLJ11078 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11078 BINDING SITE, designated SEQ ID:20310, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26503] Another function of VGAM634 is therefore inhibition of FLJ11078 (Accession NM\_018316). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11078. FLJ12783 (Accession NM\_031426) is another VGAM634 host target gene. FLJ12783 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12783, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12783 BINDING SITE, designated SEQ ID:25421, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26504] Another function of VGAM634 is therefore inhibition of

FLJ12783 (Accession NM\_031426). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12783. FLJ14327 (Accession NM\_024912) is another VGAM634 host target gene. FLJ14327 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14327, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14327 BINDING SITE, designated SEQ ID:24422, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26505] Another function of VGAM634 is therefore inhibition of FLJ14327 (Accession NM\_024912). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14327. FLJ20345 (Accession NM\_017777) is another VGAM634 host target gene. FLJ20345 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20345, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ20345 BINDING SITE, designated SEQ ID:19406, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26506] Another function of VGAM634 is therefore inhibition of FLJ20345 (Accession NM\_017777). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20345. FLJ21369 (Accession NM\_024802) is another VGAM634 host target gene. FLJ21369 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21369, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21369 BINDING SITE, designated SEQ ID:24184, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26507] Another function of VGAM634 is therefore inhibition of FLJ21369 (Accession NM\_024802). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21369. FLJ23233 (Accession NM\_024691) is another VGAM634

host target gene. FLJ23233 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23233, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23233 BINDING SITE, designated SEQ ID:24001, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26508] Another function of VGAM634 is therefore inhibition of FLJ23233 (Accession NM\_024691). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23233. KIAA0993 (Accession XM\_034413) is another VGAM634 host target gene. KIAA0993 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0993, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0993 BINDING SITE, designated SEQ ID:32084, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26509] Another function of VGAM634 is therefore inhibition of KIAA0993 (Accession XM\_034413). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0993. KIAA1040 (Accession XM\_051091) is another VGAM634 host target gene. KIAA1040 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1040 BINDING SITE, designated SEQ ID:35746, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.



[26510] Another function of VGAM634 is therefore inhibition of KIAA1040 (Accession XM\_051091). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1040. KIAA1069 (Accession XM\_042635) is another VGAM634 host target gene. KIAA1069 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1069, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1069 BINDING SITE, designated SEQ ID:33728, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26511] Another function of VGAM634 is therefore inhibition of KIAA1069 (Accession XM\_042635). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1069. KIAA1613 (Accession XM\_035946) is another VGAM634 host target gene. KIAA1613 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1613, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1613 BINDING SITE, designated SEQ ID:32361, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26512] Another function of VGAM634 is therefore inhibition of KIAA1613 (Accession XM\_035946). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1613. MGC2550 (Accession NM\_024071) is another VGAM634 host target gene. MGC2550 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2550, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2550 BINDING SITE, designated SEQ ID:23500, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26513] Another function of VGAM634 is therefore inhibition of MGC2550 (Accession NM\_024071). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

MGC2550. MGC26954 (Accession NM\_145025) is another VGAM634 host target gene. MGC26954 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC26954, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC26954 BINDING SITE, designated SEQ ID:29640, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26514] Another function of VGAM634 is therefore inhibition of MGC26954 (Accession NM\_145025). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC26954. PRO0365 (Accession NM\_014126) is another VGAM634 host target gene. PRO0365 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRO0365, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0365 BINDING SITE, designated SEQ ID:15391, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM

RNA, also designated SEQ ID:3345.

[26515] Another function of VGAM634 is therefore inhibition of PRO0365 (Accession NM\_014126). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0365. SGP28 (Accession NM\_006061) is another VGAM634 host target gene. SGP28 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SGP28, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SGP28 BINDING SITE, designated SEQ ID:12704, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26516] Another function of VGAM634 is therefore inhibition of SGP28 (Accession NM\_006061). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SGP28. LOC120856 (Accession XM\_058509) is another VGAM634 host target gene. LOC120856 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC120856, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120856 BINDING SITE, designated SEQ ID:36645, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26517] Another function of VGAM634 is therefore inhibition of LOC120856 (Accession XM\_058509). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120856. LOC144079 (Accession XM\_084711) is another VGAM634 host target gene. LOC144079 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144079, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144079 BINDING SITE, designated SEQ ID:37674, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26518] Another function of VGAM634 is therefore inhibition of LOC144079 (Accession XM\_084711). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC144079. LOC146184 (Accession XM\_096942) is another VGAM634 host target gene. LOC146184 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC146184, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146184 BINDING SITE, designated SEQ ID:40660, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26519] Another function of VGAM634 is therefore inhibition of LOC146184 (Accession XM\_096942). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146184. LOC147077 (Accession XM\_085699) is another VGAM634 host target gene. LOC147077 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC147077, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147077 BINDING SITE, designated SEQ ID:38295, to

the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26520] Another function of VGAM634 is therefore inhibition of LOC147077 (Accession XM\_085699). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147077. LOC148046 (Accession XM\_097375) is another VGAM634 host target gene. LOC148046 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148046, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148046 BINDING SITE, designated SEQ ID:40865, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26521] Another function of VGAM634 is therefore inhibition of LOC148046 (Accession XM\_097375). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148046. LOC152674 (Accession XM\_098251) is another VGAM634 host target gene. LOC152674 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC152674, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152674 BINDING SITE, designated SEQ ID:41541, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26522] Another function of VGAM634 is therefore inhibition of LOC152674 (Accession XM\_098251). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152674. LOC153222 (Accession XM\_087631) is another VGAM634 host target gene. LOC153222 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153222, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153222 BINDING SITE, designated SEQ ID:39368, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26523] Another function of VGAM634 is therefore inhibition of LOC153222 (Accession XM\_087631). Accordingly, utilities



of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153222. LOC153711 (Accession XM\_098419) is another VGAM634 host target gene. LOC153711 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153711, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153711 BINDING SITE, designated SEQ ID:41669, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26524] Another function of VGAM634 is therefore inhibition of LOC153711 (Accession XM\_098419). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153711. LOC157624 (Accession XM\_098801) is another VGAM634 host target gene. LOC157624 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157624, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC157624 BINDING SITE, designated SEQ ID:41828, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26525] Another function of VGAM634 is therefore inhibition of LOC157624 (Accession XM\_098801). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157624. LOC157867 (Accession XM\_098831) is another VGAM634 host target gene. LOC157867 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157867, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157867 BINDING SITE, designated SEQ ID:41855, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26526] Another function of VGAM634 is therefore inhibition of LOC157867 (Accession XM\_098831). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157867. LOC196264 (Accession XM\_113683) is another VGAM634 host target gene. LOC196264 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196264, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196264 BINDING SITE, designated SEQ ID:42338, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26527] Another function of VGAM634 is therefore inhibition of LOC196264 (Accession XM\_113683). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196264. LOC219899 (Accession XM\_166173) is another VGAM634 host target gene. LOC219899 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219899, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219899 BINDING SITE, designated SEQ ID:43994, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26528] Another function of VGAM634 is therefore inhibition of

LOC219899 (Accession XM\_166173). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219899. LOC253187 (Accession XM\_173139) is another VGAM634 host target gene. LOC253187 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253187, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253187 BINDING SITE, designated SEQ ID:46394, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26529] Another function of VGAM634 is therefore inhibition of LOC253187 (Accession XM\_173139). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253187. LOC90750 (Accession XM\_033868) is another VGAM634 host target gene. LOC90750 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of LOC90750 BINDING SITE, designated SEQ ID:31972, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26530] Another function of VGAM634 is therefore inhibition of LOC90750 (Accession XM\_033868). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90750. LOC91133 (Accession XM\_036372) is another VGAM634 host target gene. LOC91133 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91133, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91133 BINDING SITE, designated SEQ ID:32431, to the nucleotide sequence of VGAM634 RNA, herein designated VGAM RNA, also designated SEQ ID:3345.

[26531] Another function of VGAM634 is therefore inhibition of LOC91133 (Accession XM\_036372). Accordingly, utilities of VGAM634 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91133. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 635 (VGAM635) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26532] VGAM635 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM635 was detected is described hereinabove with reference to Figs. 1–8.

[26533] VGAM635 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cherry Mottle Leaf Virus. VGAM635 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26534] VGAM635 gene encodes a VGAM635 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM635 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM635 precursor RNA is designated SEQ ID:621, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:621 is

located at position 457 relative to the genome of Cherry Mottle Leaf Virus.

[26535] VGAM635 precursor RNA folds onto itself, forming VGAM635 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26536] An enzyme complex designated DICER COMPLEX, `dices` the VGAM635 folded precursor RNA into VGAM635 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM635 RNA is designated SEQ ID:3346, and is provided hereinbelow with reference to the sequence listing part.

[26537] VGAM635 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM635 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM635 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[26538] VGAM635 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM635 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM635 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM635 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM635 host target RNA,



herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26539] The complementary binding of VGAM635 RNA, herein designated VGAM RNA, to host target binding sites on VGAM635 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM635 host target RNA into VGAM635 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26540] It is appreciated that VGAM635 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM635 host target genes. The mRNA of each one of this plurality of VGAM635 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM635 RNA, herein designated VGAM RNA, and which when bound by VGAM635 RNA causes inhibition of translation of respective one or more VGAM635

host target proteins.

[26541] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM635 gene, herein designated VGAM GENE, on one or more VGAM635 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26542] It is yet further appreciated that a function of VGAM635 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM635 include diagnosis, prevention and treatment of viral infection by Cherry Mottle Leaf Virus.

Specific functions, and accordingly utilities, of VGAM635 correlate with, and may be deduced from, the identity of the host target genes which VGAM635 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26543] Nucleotide sequences of the VGAM635 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM635 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM635 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM635 are further described hereinbelow with reference to Table 1.

[26544] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM635 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM635 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26545] As mentioned hereinabove with reference to Fig. 1, a function of VGAM635 gene, herein designated VGAM is inhibition of expression of VGAM635 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM635 correlate with, and may be deduced from, the identity of the target genes which VGAM635 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26546] MGC5370 (Accession NM\_032739) is a VGAM635 host target gene. MGC5370 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC5370, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5370 BINDING SITE, designated SEQ ID:26469, to the nucleotide sequence of VGAM635 RNA, herein designated VGAM RNA, also designated SEQ ID:3346.

[26547] A function of VGAM635 is therefore inhibition of MGC5370 (Accession NM\_032739). Accordingly, utilities of VGAM635 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5370. LOC139522 (Accession XM\_066738) is another VGAM635 host target gene. LOC139522 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC139522, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC139522 BINDING SITE, designated SEQ ID:37344, to the nucleotide sequence of VGAM635 RNA, herein designated VGAM RNA, also designated SEQ ID:3346.

[26548] Another function of VGAM635 is therefore inhibition of LOC139522 (Accession XM\_066738). Accordingly, utilities of VGAM635 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC139522. LOC158382 (Accession XM\_098931) is another VGAM635 host target gene. LOC158382 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158382, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158382 BINDING SITE, designated SEQ ID:41965, to the nucleotide sequence of VGAM635 RNA, herein designated VGAM RNA, also designated SEQ ID:3346.

[26549] Another function of VGAM635 is therefore inhibition of LOC158382 (Accession XM\_098931). Accordingly, utilities of VGAM635 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC158382. LOC219920 (Accession XM\_167787) is another VGAM635 host target gene. LOC219920 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219920, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219920 BINDING SITE, designated SEQ ID:44805, to the nucleotide sequence of VGAM635 RNA, herein designated VGAM RNA, also designated SEQ ID:3346.

[26550] Another function of VGAM635 is therefore inhibition of LOC219920 (Accession XM\_167787). Accordingly, utilities of VGAM635 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219920. LOC63928 (Accession NM\_022097) is another VGAM635 host target gene. LOC63928 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC63928, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC63928 BINDING SITE, designated SEQ ID:22637, to the nucleotide sequence of VGAM635 RNA, herein designated

VGAM RNA, also designated SEQ ID:3346.

[26551] Another function of VGAM635 is therefore inhibition of LOC63928 (Accession NM\_022097). Accordingly, utilities of VGAM635 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC63928. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 636 (VGAM636) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26552] VGAM636 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM636 was detected is described hereinabove with reference to Figs. 1–8.

[26553] VGAM636 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cherry Mottle Leaf Virus. VGAM636 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26554] VGAM636 gene encodes a VGAM636 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM636 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM636 precursor RNA is designated SEQ ID:622, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:622 is located at position 3861 relative to the genome of Cherry Mottle Leaf Virus.

[26555] VGAM636 precursor RNA folds onto itself, forming VGAM636 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26556] An enzyme complex designated DICER COMPLEX, `dices` the VGAM636 folded precursor RNA into VGAM636 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex



comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM636 RNA is designated SEQ ID:3347, and is provided hereinbelow with reference to the sequence listing part.

[26557] VGAM636 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM636 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM636 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26558] VGAM636 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM636 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM636 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM636 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM636 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26559] The complementary binding of VGAM636 RNA, herein designated VGAM RNA, to host target binding sites on VGAM636 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM636 host target RNA into VGAM636 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26560] It is appreciated that VGAM636 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM636 host target genes. The mRNA of

each one of this plurality of VGAM636 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM636 RNA, herein designated VGAM RNA, and which when bound by VGAM636 RNA causes inhibition of translation of respective one or more VGAM636 host target proteins.

[26561] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM636 gene, herein designated VGAM GENE, on one or more VGAM636 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[26562] It is yet further appreciated that a function of VGAM636 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of viral infection by Cherry Mottle Leaf Virus. Specific functions, and accordingly utilities, of VGAM636 correlate with, and may be deduced from, the identity of the host target genes which VGAM636 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26563] Nucleotide sequences of the VGAM636 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM636 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM636 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM636 are further described hereinbelow with reference to Table 1.

[26564] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM636 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM636 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[26565] As mentioned hereinabove with reference to Fig. 1, a function of VGAM636 gene, herein designated VGAM is inhibition of expression of VGAM636 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM636 correlate with, and may be deduced from, the identity of the target genes which VGAM636 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26566] Glucose-6-phosphatase, Catalytic (glycogen storage disease type I, von Gierke disease) (G6PC, Accession NM\_000151) is a VGAM636 host target gene. G6PC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by G6PC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of G6PC BINDING SITE, designated SEQ ID:5661, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26567] A function of VGAM636 is therefore inhibition of Glucose-6-phosphatase, Catalytic (glycogen storage disease type I,

von Gierke disease) (G6PC, Accession NM\_000151). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with G6PC. Membrane-spanning 4-domains, Subfamily A, Member 2 (Fc fragment of IgE, high affinity I, receptor for; beta polypeptide) (MS4A2, Accession NM\_021950) is another VGAM636 host target gene. MS4A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MS4A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MS4A2 BINDING SITE, designated SEQ ID:22477, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26568] Another function of VGAM636 is therefore inhibition of Membrane-spanning 4-domains, Subfamily A, Member 2 (Fc fragment of IgE, high affinity I, receptor for; beta polypeptide) (MS4A2, Accession NM\_021950), a gene which binds to the fc region of immunoglobulins epsilon. Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with MS4A2. The function of MS4A2 has been established by previous studies. Shirakawa et al. (1994) reported a significant association between atopy and substitution of a leucine for an isoleucine at position 181 of the FCER1B gene product. Hizawa et al. (1995) failed to find this leu181-to-ile substitution. Folster-Holst et al. (1998) presented evidence from linkage studies in 12 families with atopic dermatitis for linkage in close proximity to the marker D11S903. The method of analysis suggested an oligogenic mode of inheritance as well as heterogeneity in the genetic susceptibility to atopy and atopic dermatitis; only 2 of 12 families showed evidence for linkage using the oligogenic model.

[26569] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26570] Folster-Holst, R.; Moises, H. W.; Yang, L.; Fritsch, W.; Weissenbach, J.; Christophers, E. : Linkage between atopy and the IgE high-affinity receptor gene at 11q13 in atopic dermatitis families. Hum. Genet. 102: 236-239, 1998. ; and

[26571] Shirakawa, T.; Li, A.; Dubowitz, M.; Dekker, J. W.; Shaw, A. E.; Faux, J. A.; Ra, C.; Cookson, W. O. C. M.; Hopkin, J. M. :

Association between atopy and variants of the beta sub-unit of.

[26572] Further studies establishing the function and utilities of MS4A2 are found in John Hopkins OMIM database record ID 147138, and in cited publications numbered 11465–11466, 3386, 11467–11469, 338 and 11470–11472 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Oxytocin Receptor (OXTR, Accession NM\_000916) is another VGAM636 host target gene. OXTR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OXTR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OXTR BINDING SITE, designated SEQ ID:6623, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26573] Another function of VGAM636 is therefore inhibition of Oxytocin Receptor (OXTR, Accession NM\_000916), a gene which induces inward ion currents. Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OXTR. The



function of OXTR has been established by previous studies. Just before the onset of labor, uterine muscle becomes exceedingly sensitive to oxytocin, for which it is a primary target tissue, because of a dramatic increase in the number of oxytocin receptors. Kimura et al. (1992) reported the structure and expression of the human oxytocin receptor cDNA isolated by expression cloning. The encoded receptor was a 388-amino acid polypeptide with 7 transmembrane domains typical of G protein-coupled receptors. The oxytocin receptor, expressed in *Xenopus* oocytes, specifically responded to oxytocin and induced an inward membrane current. Messenger RNAs for the receptor were of 2 sizes, 3.6 kb in breast and 4.4 kb in ovary, endometrium, and myometrium. The mRNA level in myometrium was very high at term. Yang et al. (2002) found that mutation of lysine-270 (K270) in wildtype OTR completely abolished the ability of the receptor to stimulate phosphatidylinositide turnover, with only a small reduction in ligand affinity. These data demonstrated that OTR K270 is critically important in the stimulation by OTR of phosphatidylinositide turnover. Mutation of K270 also adversely affected the ability of OTR to stimulate ERK1/2 (601795, 176948) phosphorylation. Therefore, this

residue plays an important role in the specificity of OTR/G- $\alpha$ -q (OMIM Ref. No. 600998)/PLC (see OMIM Ref. No. 602142) coupling.

[26574] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26575] Kimura, T.; Tanizawa, O.; Mori, K.; Brownstein, M. J.; Okayama, H. : Structure and expression of a human oxytocin receptor. *Nature* 356: 526–529, 1992. ; and

[26576] Yang, M.; Wang, W.; Zhong, M.; Philippi, A.; Lichtarge, O.; Sanborn, B. M. : Lysine 270 in the third intracellular domain of the oxytocin receptor is an important determinant for G- $\alpha$ ph.

[26577] Further studies establishing the function and utilities of OXTR are found in John Hopkins OMIM database record ID 167055, and in cited publications numbered 3154–3157 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Serine (or cysteine) Proteinase Inhibitor, Clade B (ovalbumin), Member 9 (SERPINB9, Accession NM\_004155) is another VGAM636 host target gene. SERPINB9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SERPINB9, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SERPINB9 BINDING SITE, designated SEQ ID:10365, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26578] Another function of VGAM636 is therefore inhibition of Serine (or cysteine) Proteinase Inhibitor, Clade B (ovalbumin), Member 9 (SERPINB9, Accession NM\_004155), a gene which may be a serpin serine protease inhibitor that interacts with granzyme B (GZMB). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SERPINB9. The function of SERPINB9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM60. Wingless-type MMTV Integration Site Family, Member 8B (WNT8B, Accession XM\_005702) is another VGAM636 host target gene. WNT8B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WNT8B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of WNT8B BINDING SITE, designated SEQ ID:29984, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26579] Another function of VGAM636 is therefore inhibition of Wingless-type MMTV Integration Site Family, Member 8B (WNT8B, Accession XM\_005702), a gene which is the ligand for members of the frizzled family of seven trans-membrane receptors and may play an important role in the development and differentiation of certain forebrain structures. Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WNT8B. The function of WNT8B has been established by previous studies. WNT genes encode intercellular signaling glycoproteins that play important roles in key processes of embryonic development such as mesoderm induction, specification of the embryonic axis, and patterning of the central nervous system, spinal cord, and limbs. The name WNT denotes the relationship of this family to the *Drosophila* segment polarity gene 'wingless,' and to its vertebrate ortholog Int1, a mouse protooncogene; see WNT1 (OMIM Ref. No.

164820). Lako et al. (1996) noted that multiple WNT genes are known to exist in several species that have been investigated ranging from *Drosophila* to man. They have been classified into various groups and subgroups on the basis of high sequence homology and common expression patterns. The vertebrate WNT8 subfamily includes genes from *Xenopus*, zebrafish, and chicken; Lako et al. (1996) characterized the first mammalian WNT8 homolog, a human member of the Wnt8 family that they termed WNT8B on the basis of the very high sequence similarity (approximately 90% identity) of the inferred protein to those encoded by the *Xenopus* and zebrafish Wnt8b genes. The human cDNA encodes a polypeptide that contains a C2H2 zinc finger-like motif. Lako et al. (1998) presented the full-length cDNA sequence and genomic organization of the human WNT8B gene and reported studies of expression of the gene in human and mouse embryos. The WNT8B gene contains 6 exons separated by small introns, with the exception of intron 1. The predicted protein has 351 amino acids. The gene is expressed predominantly as a transcript of approximately 2.1 kb. The human and mouse expression patterns appeared to be identical and were restricted to the developing brain, with the

great majority of expression being found in the developing forebrain. In the latter case, expression was confined to the germinative neuroepithelium of 3 sharply delimited regions: the dorsomedial wall of the telencephalic ventricles (which includes the developing hippocampus), a discrete region of the dorsal thalamus, and the mammillary and retromammillary regions of the posterior hypothalamus. Expression in the developing hippocampus may suggest a role for WNT8B in patterning of this region. By use of PCR typing of a human monochromosomal hybrid cell panel, Lako et al. (1996) mapped the WNT8B gene to chromosome 10. They refined the localization to 10q24 by fluorescence in situ hybridization. Lako et al. (1998) suggested WNT8B as a candidate gene for partial epilepsy (EPT; 600512) in families in which the disease has been linked to markers in the 10q23–q24 region.

[26580] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26581] Lako, M.; Lindsay, S.; Bullen, P.; Wilson, D. I.; Robson, S. C.; Strachan, T. : A novel mammalian Wnt gene, WNT8B, shows brain–restricted expression in early development, with sharply delimited expression boundaries in the de–

veloping forebrain. Hum. Molec. Genet. 7: 813–822, 1998.

; and

[26582] Lako, M.; Strachan, T.; Curtis, A. R. J.; Lindsay, S. : Isolation and characterization of WNT8B, a novel human Wnt gene that maps to 10q24. Genomics 35: 386–388, 1996.

[26583] Further studies establishing the function and utilities of WNT8B are found in John Hopkins OMIM database record ID 601396, and in cited publications numbered 6652–6653 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0976 (Accession NM\_014917) is another VGAM636 host target gene. KIAA0976 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0976, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0976 BINDING SITE, designated SEQ ID:17169, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26584] Another function of VGAM636 is therefore inhibition of KIAA0976 (Accession NM\_014917). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0976. Smith–Magenis Syndrome Chromosome Region, Candidate 7 (SMCR7, Accession NM\_139162) is another VGAM636 host target gene. SMCR7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SMCR7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMCR7 BINDING SITE, designated SEQ ID:29170, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26585] Another function of VGAM636 is therefore inhibition of Smith–Magenis Syndrome Chromosome Region, Candidate 7 (SMCR7, Accession NM\_139162). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMCR7. LOC138307 (Accession XM\_059963) is another VGAM636 host target gene. LOC138307 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC138307, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen–



tarity of the nucleotide sequences of LOC138307 BINDING SITE, designated SEQ ID:37124, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26586] Another function of VGAM636 is therefore inhibition of LOC138307 (Accession XM\_059963). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC138307. LOC146316 (Accession XM\_027568) is another VGAM636 host target gene. LOC146316 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146316 BINDING SITE, designated SEQ ID:30524, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26587] Another function of VGAM636 is therefore inhibition of LOC146316 (Accession XM\_027568). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146316. LOC157226 (Accession XM\_033876) is an-

other VGAM636 host target gene. LOC157226 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC157226, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157226 BINDING SITE, designated SEQ ID:31978, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26588] Another function of VGAM636 is therefore inhibition of LOC157226 (Accession XM\_033876). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157226. LOC158714 (Accession XM\_088650) is another VGAM636 host target gene. LOC158714 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC158714, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158714 BINDING SITE, designated SEQ ID:39884, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26589] Another function of VGAM636 is therefore inhibition of LOC158714 (Accession XM\_088650). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158714. LOC254082 (Accession XM\_173165) is another VGAM636 host target gene. LOC254082 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254082, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254082 BINDING SITE, designated SEQ ID:46422, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26590] Another function of VGAM636 is therefore inhibition of LOC254082 (Accession XM\_173165). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254082. LOC51634 (Accession NM\_016024) is another VGAM636 host target gene. LOC51634 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51634, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51634 BINDING SITE, designated SEQ ID:18101, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26591] Another function of VGAM636 is therefore inhibition of LOC51634 (Accession NM\_016024). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51634. LOC92017 (Accession XM\_042234) is another VGAM636 host target gene. LOC92017 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92017 BINDING SITE, designated SEQ ID:33711, to the nucleotide sequence of VGAM636 RNA, herein designated VGAM RNA, also designated SEQ ID:3347.

[26592] Another function of VGAM636 is therefore inhibition of LOC92017 (Accession XM\_042234). Accordingly, utilities of VGAM636 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC92017. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 637 (VGAM637) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26593] VGAM637 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM637 was detected is described hereinabove with reference to Figs. 1–8.

[26594] VGAM637 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Frog Adenovirus 1. VGAM637 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26595] VGAM637 gene encodes a VGAM637 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM637 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM637 precursor RNA is designated SEQ ID:623, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:623 is located at position 5382 relative to the genome of Frog Adenovirus 1.

[26596] VGAM637 precursor RNA folds onto itself, forming VGAM637 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26597] An enzyme complex designated DICER COMPLEX, `dices` the VGAM637 folded precursor RNA into VGAM637 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM637 RNA is designated SEQ ID:3348, and is provided hereinbelow with reference to the sequence listing part.

[26598] VGAM637 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM637 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM637 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26599] VGAM637 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM637 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM637 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM637 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM637 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26600] The complementary binding of VGAM637 RNA, herein designated VGAM RNA, to host target binding sites on VGAM637 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM637 host target RNA into VGAM637 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26601] It is appreciated that VGAM637 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM637 host target genes. The mRNA of each one of this plurality of VGAM637 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM637 RNA, herein designated VGAM RNA, and which when bound by VGAM637 RNA causes in-



hibition of translation of respective one or more VGAM637 host target proteins.

[26602] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM637 gene, herein designated VGAM GENE, on one or more VGAM637 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26603] It is yet further appreciated that a function of VGAM637 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM637 include diagnosis, prevention and

treatment of viral infection by Frog Adenovirus 1. Specific functions, and accordingly utilities, of VGAM637 correlate with, and may be deduced from, the identity of the host target genes which VGAM637 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26604] Nucleotide sequences of the VGAM637 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM637 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM637 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM637 are further described hereinbelow with reference to Table 1.

[26605] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM637 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM637 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26606] As mentioned hereinabove with reference to Fig. 1, a function of VGAM637 gene, herein designated VGAM is inhibition of expression of VGAM637 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM637 correlate with, and may be deduced from, the identity of the target genes which VGAM637 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26607] FREB (Accession NM\_032738) is a VGAM637 host target gene. FREB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FREB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FREB BINDING SITE, designated SEQ ID:26465, to the nucleotide sequence of VGAM637 RNA, herein designated VGAM RNA, also designated SEQ ID:3348.

[26608] A function of VGAM637 is therefore inhibition of FREB (Accession NM\_032738). Accordingly, utilities of VGAM637 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FREB. Tumor Necrosis Factor (ligand) Superfamily, Member 10 (TNFSF10, Accession NM\_003810) is another VGAM637 host target gene. TNFSF10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFSF10, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFSF10 BINDING SITE, designated SEQ ID:9899, to the nucleotide sequence of VGAM637 RNA, herein designated VGAM RNA, also designated SEQ ID:3348.

[26609] Another function of VGAM637 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 10 (TNFSF10, Accession NM\_003810), a gene which mediates cell death. Accordingly, utilities of VGAM637 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFSF10. The function of TNFSF10 has been established by previous studies. Degli-Esposti et al. (1997) noted that TRAIL can induce apoptosis in a wide variety of transformed cell lines of diverse lineage, but does not appear to kill normal cells even though TRAIL mRNA is expressed at significant levels in most normal tissues. They suggested that the regulation of TRAIL function takes place at the level of receptor expression. The TRAIL receptors TRAILR1, also called DR4 (OMIM Ref. No. 603611), and TRAILR2, also called DR5 (OMIM Ref. No. 603612), are capable of mediating apoptosis. Two other receptors, TRAILR3 (OMIM Ref. No.

603613) and TRAILR4 (OMIM Ref. No. 603614), do not signal apoptosis and are potential decoy receptors for TRAIL. Cell death induced by TRAIL had been believed to occur exclusively in tumor cells, suggesting that this drug was safe to use as an antitumor therapy. Nitsch et al. (2000) reported that TRAIL induced apoptosis in the human brain, which argues against the use of TRAIL for therapy of human brain tumors. However, neuroinflammatory T cells that express TRAIL might induce apoptosis of brain tissue, indicating a potential target for treatment of multiple sclerosis. Animal model experiments lend further support to the function of TNFSF10. Cretney et al. (2002) generated healthy, fertile Trail-deficient mice by homologous recombination. Functional analysis confirmed the importance of Trail in mediating natural killer (NK) cytotoxicity to some tumor target cells. The authors found that Trail contributes to NK cell suppression of metastases to liver by a renal adenocarcinoma and to multiple tissues by breast carcinoma cells. Trail  $-/-$  mice were also more susceptible than wildtype mice to early onset of fibrosarcomas from lower doses of methylcholanthrene.

[26610] It is appreciated that the abovementioned animal model for TNFSF10 is acknowledged by those skilled in the art as

a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[26611] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26612] Degli-Esposti, M. A.; Dougall, W. C.; Smolak, P. J.; Waugh, J. Y.; Smith, C. A.; Goodwin, R. G. : The novel receptor TRAIL-R4 induces NF-kappa-B and protects against TRAIL-mediated apoptosis, yet retains an incomplete death domain. *Immunity* 7: 813-820, 1997. ; and

[26613] Nitsch, R.; Bechmann, I.; Deisz, R. A.; Haas, D.; Lehmann, T. N.; Wendling, U.; Zipp, F. : Human brain-cell death induced by tumour-necrosis-factor-related apoptosis-inducing ligand (TRA.

[26614] Further studies establishing the function and utilities of TNFSF10 are found in John Hopkins OMIM database record ID 603598, and in sited publications numbered 5312-5313, 5880, 5963-5965, 60 and 5966 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0323 (Accession XM\_032634) is another VGAM637 host target gene. KIAA0323 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

KIAA0323, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0323 BINDING SITE, designated SEQ ID:31687, to the nucleotide sequence of VGAM637 RNA, herein designated VGAM RNA, also designated SEQ ID:3348.

[26615] Another function of VGAM637 is therefore inhibition of KIAA0323 (Accession XM\_032634). Accordingly, utilities of VGAM637 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0323. LOC254251 (Accession XM\_171088) is another VGAM637 host target gene. LOC254251 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254251 BINDING SITE, designated SEQ ID:45893, to the nucleotide sequence of VGAM637 RNA, herein designated VGAM RNA, also designated SEQ ID:3348.

[26616] Another function of VGAM637 is therefore inhibition of LOC254251 (Accession XM\_171088). Accordingly, utilities

of VGAM637 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254251. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 638 (VGAM638) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26617] VGAM638 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM638 was detected is described hereinabove with reference to Figs. 1–8.

[26618] VGAM638 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turnip Mosaic Virus. VGAM638 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26619] VGAM638 gene encodes a VGAM638 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM638 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–



quence of VGAM638 precursor RNA is designated SEQ ID:624, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:624 is located at position 6990 relative to the genome of Turnip Mosaic Virus.

[26620] VGAM638 precursor RNA folds onto itself, forming VGAM638 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26621] An enzyme complex designated DICER COMPLEX, `dices` the VGAM638 folded precursor RNA into VGAM638 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 51%) nucleotide sequence of VGAM638 RNA is designated SEQ ID:3349, and

is provided hereinbelow with reference to the sequence listing part.

[26622] VGAM638 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM638 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM638 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26623] VGAM638 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM638 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM638 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM638 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM638 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26624] The complementary binding of VGAM638 RNA, herein designated VGAM RNA, to host target binding sites on VGAM638 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM638 host target RNA into VGAM638 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26625] It is appreciated that VGAM638 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM638 host target genes. The mRNA of each one of this plurality of VGAM638 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM638 RNA, herein designated VGAM RNA, and which when bound by VGAM638 RNA causes inhibition of translation of respective one or more VGAM638 host target proteins.

[26626] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM638 gene, herein designated VGAM GENE, on one or more VGAM638 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26627] It is yet further appreciated that a function of VGAM638 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of viral infection by Turnip Mosaic Virus. Specific functions, and accordingly utilities, of VGAM638 correlate with, and may be deduced from, the identity of the host target genes which VGAM638 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26628] Nucleotide sequences of the VGAM638 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM638 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM638 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM638 are further described hereinbelow with reference to Table 1.

[26629] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM638 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM638 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26630] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM638 gene, herein designated VGAM is inhibition of expression of VGAM638 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM638 correlate with, and may be deduced from, the identity of the target genes which VGAM638 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26631] V-akt Murine Thymoma Viral Oncogene Homolog 1 (AKT1, Accession NM\_005163) is a VGAM638 host target gene. AKT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKT1 BINDING SITE, designated SEQ ID:11650, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26632] A function of VGAM638 is therefore inhibition of V-akt Murine Thymoma Viral Oncogene Homolog 1 (AKT1, Accession NM\_005163), a gene which Serine-threonine protein kinase. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKT1. The function of AKT1

and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM188. Rho GTPase Activating Protein 6 (ARHGAP6, Accession NM\_001174) is another VGAM638 host target gene. ARHGAP6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGAP6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP6 BINDING SITE, designated SEQ ID:6841, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26633] Another function of VGAM638 is therefore inhibition of Rho GTPase Activating Protein 6 (ARHGAP6, Accession NM\_001174), a gene which activates the rho-type GTPases by converting them to an inactive GTP-bound state. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP6. The function of ARHGAP6 and its association with various diseases and clinical conditions, has been established by previous studies, as de-

scribed hereinabove with reference to VGAM55. Bassoon (presynaptic cytomatrix protein) (BSN, Accession NM\_003458) is another VGAM638 host target gene. BSN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BSN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BSN BINDING SITE, designated SEQ ID:9521, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26634] Another function of VGAM638 is therefore inhibition of Bassoon (presynaptic cytomatrix protein) (BSN, Accession NM\_003458), a gene which may be involved in cytomatrix organization at the site of neurotransmitter release. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BSN. The function of BSN has been established by previous studies. Both the presynaptic terminal and the postsynaptic compartment of neuronal synapses comprise a highly specialized cytoskeleton underlying the synaptic membranes. The presynaptic nerve terminal is the principal site of regulated neurotransmitter release.



The active zone is the region of the presynaptic plasmalemma over which synaptic vesicles dock, fuse, and release neurotransmitter. Piccolo (PCLO; 604918), a 420-kD protein, is 1 component of the presynaptic cytomatrix.

Tom Dieck et al. (1998) isolated a large (greater than 400 kD) protein in mouse that is also found in the presynaptic compartments of rat brain synapses. They designated the protein Bassoon because it, along with Piccolo, is part of the ensemble of presynaptic proteins that are involved in orchestrating events at the nerve terminal. Bassoon is found in axon terminals of hippocampal neurons where it is highly concentrated in the vicinity of the active zone.

Piccolo has a similar distribution and colocalizes with Bassoon in cultured hippocampal cells. Tom Dieck et al.

(1998) suggested that Bassoon may be involved in cytomatrix organization at the site of neurotransmitter re-

lease Multiple system atrophy (MSA) is a sporadic progressive neurodegenerative disease. By differential hybridization to high-density cDNA filters, Hashida et al.

(1998) identified human frontal lobe cDNAs with altered expression patterns in MSA patients. One partial cDNA whose expression was elevated 2-fold in MSA cerebella encoded a protein that the authors designated ZNF231

(zinc finger protein-231). By screening additional libraries with the partial cDNA, they assembled a full-length ZNF231 cDNA. The predicted 3,926-amino acid protein contains 2 glycine-proline dipeptide repeats, a pair of homologous C8 double zinc finger motifs, a leucine zipper motif, an SH3 domain-binding motif, 2 nuclear targeting sequences, 2 glutamine-rich domains, and a histidine-rich domain. Northern blot analysis of rat tissues indicated that the ZNF231 gene was expressed as a 16-kb mRNA specifically in brain. By RT-PCR of human brain cell lines and tissue, Hashida et al. (1998) determined that ZNF231 was expressed in the cerebellum and in a neuroblastoma cell line, but not in the white matter. Ishikawa et al. (1997) recovered a ZNF231 cDNA, designated KIAA0434, as 1 of 78 brain cDNAs that may encode large proteins. Gundelfinger (1999) stated that ZNF231 is the human homolog of Bassoon

[26635] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26636] tom Dieck, S.; Sanmarti-Vila, L.; Langnaese, K.; Richter, K.; Kindler, S.; Soyke, A.; Wex, H.; Smalla, K.-H.; Kampf, U.; Franzer, J.-T.; Stumm, M.; Garner, C. C.; Gundelfinger, E.

D. : Bassoon, a novel zinc-finger CAG/glutamine-repeat protein selectively localized at the active zone of presynaptic nerve terminals. J. Cell Biol. 142: 499–509, 1998. ; and

[26637] Hashida, H.; Goto, J.; Zhao, N.; Takahashi, N.; Hirai, M.; Kanazawa, I.; Sakaki, Y. : Cloning and mapping of ZNF231, a novel brain-specific gene encoding neuronal double zinc finger prot.

[26638] Further studies establishing the function and utilities of BSN are found in John Hopkins OMIM database record ID 604020, and in cited publications numbered 7612–7613, 110 and 7632–7633 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Deiodinase, Iodothyronine, Type III (DIO3, Accession NM\_001362) is another VGAM638 host target gene. DIO3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DIO3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DIO3 BINDING SITE, designated SEQ ID:7042, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26639] Another function of VGAM638 is therefore inhibition of Deiodinase, Iodothyronine, Type III (DIO3, Accession NM\_001362), a gene which regulates circulating fetal thyroid hormone concentrations . Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIO3. The function of DIO3 has been established by previous studies. Thyroid hormone is critical to the normal development of the human central nervous system. Salvatore et al. (1995) noted that, despite the presence of thyroxine (T4) and thyroid follicles in the fetal thyroid by 10 to 12 weeks of gestation, as well as the potential availability of maternal thyroid hormone, the free concentration of the active thyroid hormone T3 is less than half that of maternal levels up to the time of delivery. The physiologic rationale for this circumstance is not well understood, but the authors suggested that it is possible that 'normal' circulating T3 concentrations could have deleterious effects on immature tissues or could enhance the metabolic requirements of the fetus. There are 2 principal mechanisms by which the circulating fetal T3 concentration is maintained at low levels. One is that the type I iodothyronine deiodinase (OMIM Ref. No. 147892) in fetal liver is expressed at

lower levels relative to those in adult life. This reduces the extra thyroidal T3 supply from this source. The second important factor in maintaining low serum T3 concentrations is the expression of high levels of the type III deiodinase in placenta of all species examined. Type III iodothyronine deiodinase catalyzes the conversion of T4 and T3 to inactive metabolites. Salvatore et al. (1995) cloned human placental type III iodothyronine deiodinase (which they referred to as D3). It is a selenoenzyme, as evidenced by (1) the presence of an in-frame UGA codon at position 144; (2) the synthesis of a 32-kD (75)Se-labeled protein in D3 cDNA transfected cells; and (3) the presence of a selenocysteine insertion sequence element in the 3-prime untranslated region of an mRNA that is required for its expression. The authors stated that the D3 selenocysteine insertion sequence element is more potent than that found in the type I deiodinase or glutathione peroxidase (OMIM Ref. No. 138320) gene, suggesting a high priority for selenocysteine incorporation into this enzyme. The conservation of this enzyme from *Xenopus laevis* tadpoles to humans implies an essential role for regulation of thyroid hormone inactivation during embryologic development. Huang et al. (2000) reported the case of a

3-month-old infant with massive hepatic hemangiomas and primary hypothyroidism who needed very high doses of thyroid hormone to restore euthyroidism and normal thyrotropin secretion. This finding suggested that the rate of degradation of thyroid hormone was accelerated. They subsequently identified high levels of type III iodothyronine deiodinase activity in the hemangioma tissue. Normally present in the brain and placenta, this selenoenzyme catalyzes the conversion of thyroxine to reverse triiodothyronine and the conversion of triiodothyronine to 3,3-prime-diiodothyronine, both of which are biologically inactive. They then retrospectively analyzed other patients with hemangiomas and identified additional patients with similar histories and other hemangiomas with type III iodothyronine deiodinase activity.

[26640] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26641] Hernandez, A.; Park, J. P.; Lyon, G. J.; Mohandas, T. K.; St. Germain, D. L. : Localization of the type 3 iodothyronine deiodinase (DIO3) gene to human chromosome 14q32 and mouse chromosome 12F1. *Genomics* 53: 119–121, 1998.  
; and

[26642] Huang, S. A.; Tu, H. M.; Harney, J. W.; Venihaki, M.; Butte, A. J.; Kozakewich, H. P. W.; Fishman, S. J.; Larsen, P. R. : Severe hypothyroidism caused by type 3 iodothyronine deiodinase.

[26643] Further studies establishing the function and utilities of DIO3 are found in John Hopkins OMIM database record ID 601038, and in cited publications numbered 6871–6873 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ferritin, Heavy Polypeptide 1 (FTH1, Accession XM\_042852) is another VGAM638 host target gene. FTH1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FTH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FTH1 BINDING SITE, designated SEQ ID:33808, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26644] Another function of VGAM638 is therefore inhibition of Ferritin, Heavy Polypeptide 1 (FTH1, Accession XM\_042852), a gene which stores iron in a soluble, non-toxic, readily available form. Accordingly, utilities of

VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FTH1. The function of FTH1 has been established by previous studies. Synthesis of both the H- and L-ferritin subunits is controlled by a common cytosolic protein, iron regulatory protein (IRP), which binds to the iron-responsive element (IRE) in the 5-prime untranslated region of the H- and L-ferritin mRNAs (Leibold and Munro, 1988; Eisenstein, 2000). In 4 of 7 members of a Japanese family affected by dominantly inherited iron overload, Kato et al. (2001) found a single point mutation (A49U; 134770.0001) in the IRE motif of H ferritin mRNA. Gel-shift mobility assay and Scatchard-plot analysis revealed that a mutated IRE probe had a higher binding affinity to IRP than did the wildtype probe. When mutated H subunit was overexpressed in COS1 cells, suppression of H-subunit synthesis and of the increment of radiolabeled iron uptake were observed. These data suggested that the A49U mutation in the IRE of H-subunit is responsible for tissue iron deposition and is a novel cause of hereditary iron overload, most likely related to impairment of the ferroxidase activity generated by H subunit. Animal model experiments lend further support to the function of FTH1. Ferreira et al. (2000) dis-



rupted the H ferritin gene in mice by homologous recombination. Heterozygous mice were healthy, fertile, and did not differ significantly from their control littermates.

However, Fth  $-/-$  embryos died between 3.5 and 9.5 days of development, suggesting that there is no functional redundancy between the 2 ferritin subunits and that, in the absence of H subunits, L ferritin homopolymers are not able to maintain iron in a bioavailable and nontoxic form. The pattern of expression of the wildtype Fth gene in 9.5-day embryos is restricted to the developing heart and central nervous system.

[26645] It is appreciated that the abovementioned animal model for FTH1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[26646] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26647] Ferreira, C.; Bucchini, D.; Martin, M.-E.; Levi, S.; Arosio, P.; Grandchamp, B.; Beaumont, C. : Early embryonic lethality of H ferritin gene deletion in mice. J. Biol. Chem. 275: 3021–3024, 2000. ; and

[26648] Kato, J.; Fujikawa, K.; Kanda, M.; Fukuda, N.; Sasaki, K.;

Takayama, T.; Kobune, M.; Takada, K.; Takimoto, R.; Hamada, H.; Ikeda, T.; Niitsu, Y. : A mutation, in the iron-responsive el.

[26649] Further studies establishing the function and utilities of FTH1 are found in John Hopkins OMIM database record ID 134770, and in cited publications numbered 11578–11580, 3984, 11581–1159 and 11962–11970 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Gonadotropin-releasing Hormone Receptor (GNRHR, Accession NM\_000406) is another VGAM638 host target gene. GNRHR BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by GNRHR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GNRHR BINDING SITE, designated SEQ ID:5983, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26650] Another function of VGAM638 is therefore inhibition of Gonadotropin-releasing Hormone Receptor (GNRHR, Accession NM\_000406), a gene which stimulates the secre-

tion stimulates phosphoinositide turnover and membrane depolarization. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNRHR. The function of GNRHR has been established by previous studies. Kakar et al. (1992) isolated a cDNA for the GNRH receptor and showed that it encodes a protein with a transmembrane topology similar to that of other G protein-coupled 7-transmembrane-domain receptors. Grosse et al. (1997) used RT-PCR of human pituitary poly(A)<sup>+</sup> RNA to clone the full-length GNRHR gene and a second truncated cDNA characterized by a 128-bp deletion between nucleotide positions 522 and 651. The deletion causes a frameshift in the open reading frame, thus generating new coding sequence for a further 75 amino acids. The truncated cDNA arises from alternative splicing that uses a cryptic 3-prime splice site in exon 2. Translation products of approximately 45 to 50 and 42 kD were immunoprecipitated from COS-7 cells transfected with wildtype and truncated GNRHR cDNAs, respectively. The splice variant was incapable of ligand binding and signal transduction. Coexpression of wildtype and truncated proteins in transiently or stably transfected cells, resulted in impaired signaling

via the wildtype GNRHR by reducing maximal agonist-induced inositol phosphate accumulation. This inhibitory effect depended on the amount of splice variant cDNA co-transfected and was specific for GNRHR. Coexpression of the wildtype and truncated GNRHRs resulted in impaired insertion of wildtype GNRHR into the plasma membrane. Caron et al. (1999) studied a kindred with 3 sibs with isolated hypogonadotropic hypogonadism who were genetic compounds for the arg262-to-gln mutation (138850.0002) and an ala129-to-asp (138850.0004) mutation that resulted in a complete loss of function. The 2 brothers had microphallus and bilateral cryptorchidism and were referred for lack of puberty; their sister had primary amenorrhea and a complete lack of puberty. The authors concluded that these hypogonadal patients were partially resistant to pulsatile GNRH administration, suggesting that they should be treated with gonadotropins to induce spermatogenesis or ovulation rather than with pulsatile GNRH. Kottler et al. (1999) analyzed in detail the GNRHR mutations in 7 independent familial and sporadic cases of idiopathic hypogonadotropic hypogonadism reported to that time. The Q106R (138850.0001) and R262Q (138850.0002) mutations were frequent in pa-

tients from all geographic areas (North or South America or Europe).

[26651] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26652] Caron, P.; Chauvin, S.; Christin-Maitre, S.; Bennet, A.; Lahlou, N.; Counis, R.; Bouchard, P.; Kottler, M.-L. : Resistance of hypogonadic patients with mutated GnRH receptor genes to pulsatile GnRH administration. J. Clin. Endocr. Metab. 84: 990-996, 1999. ; and

[26653] Kakar, S. S.; Musgrove, L. C.; Devor, D. C.; Sellers, J. C.; Neill, J. D. : Cloning, sequencing, and expression of human gonadotropin releasing hormone (GnRH) receptor. Biochem. Biophys.

[26654] Further studies establishing the function and utilities of GNRHR are found in John Hopkins OMIM database record ID 138850, and in cited publications numbered 3917-392 and 4008-4022 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. G Protein-coupled Receptor 30 (GPR30, Accession NM\_001505) is another VGAM638 host target gene. GPR30 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR30,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR30 BINDING SITE, designated SEQ ID:7252, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26655] Another function of VGAM638 is therefore inhibition of G Protein-coupled Receptor 30 (GPR30, Accession NM\_001505), a gene which receives chemical signals in cell communication in both CNS and peripheral tissues. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR30. The function of GPR30 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM171.V-myb Myeloblastosis Viral Oncogene Homolog (avian)-like 1 (MYBL1, Accession XM\_034274) is another VGAM638 host target gene. MYBL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYBL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of MYBL1 BINDING SITE, designated SEQ ID:32041, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26656] Another function of VGAM638 is therefore inhibition of V-myb Myeloblastosis Viral Oncogene Homolog (avian)-like 1 (MYBL1, Accession XM\_034274), a gene which could have a role in the proliferation and/or differentiation of neurogenic, spermatogenic and b-lymphoid cells. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYBL1. The function of MYBL1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM184. Neurocalcin Delta (NCALD, Accession NM\_032041) is another VGAM638 host target gene. NCALD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCALD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCALD BINDING SITE, designated SEQ ID:25746, to the nucleotide sequence of VGAM638

RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26657] Another function of VGAM638 is therefore inhibition of Neurocalcin Delta (NCALD, Accession NM\_032041). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCALD. Short Stature Homeobox (SHOX, Accession NM\_006883) is another VGAM638 host target gene. SHOX BINDING SITE1 and SHOX BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SHOX, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SHOX BINDING SITE1 and SHOX BINDING SITE2, designated SEQ ID:13746 and SEQ ID:6053 respectively, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26658] Another function of VGAM638 is therefore inhibition of Short Stature Homeobox (SHOX, Accession NM\_006883). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SHOX. Thymidine Kinase 2, Mitochondrial



(TK2, Accession NM\_004614) is another VGAM638 host target gene. TK2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TK2 BINDING SITE, designated SEQ ID:10959, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26659] Another function of VGAM638 is therefore inhibition of Thymidine Kinase 2, Mitochondrial (TK2, Accession NM\_004614), a gene which phosphorylates thymidine, deoxycytidine, deoxyuridine, and also anti-viral and anti-cancer nucleoside analogs. Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TK2. The function of TK2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM210.BM-002 (Accession NM\_016617) is another VGAM638 host target gene. BM-002 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by BM-002, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BM-002 BINDING SITE, designated SEQ ID:18725, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26660] Another function of VGAM638 is therefore inhibition of BM-002 (Accession NM\_016617). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BM-002. C1q and Tumor Necrosis Factor Related Protein 3 (C1QTNF3, Accession NM\_030945) is another VGAM638 host target gene. C1QTNF3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1QTNF3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1QTNF3 BINDING SITE, designated SEQ ID:25217, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26661] Another function of VGAM638 is therefore inhibition of

C1q and Tumor Necrosis Factor Related Protein 3 (C1QTNF3, Accession NM\_030945). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1QTNF3. Carbohydrate (N-acetylglucosamine 6-O) Sulfotransferase 4 (CHST4, Accession NM\_005769) is another VGAM638 host target gene. CHST4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CHST4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST4 BINDING SITE, designated SEQ ID:12339, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26662] Another function of VGAM638 is therefore inhibition of Carbohydrate (N-acetylglucosamine 6-O) Sulfotransferase 4 (CHST4, Accession NM\_005769). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHST4. DKFZp761N1114 (Accession XM\_086327) is another VGAM638 host target gene. DKFZp761N1114 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by DKFZp761N1114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761N1114 BINDING SITE, designated SEQ ID:38605, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26663] Another function of VGAM638 is therefore inhibition of DKFZp761N1114 (Accession XM\_086327). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761N1114. FLJ14327 (Accession NM\_024912) is another VGAM638 host target gene. FLJ14327 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14327, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14327 BINDING SITE, designated SEQ ID:24427, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26664] Another function of VGAM638 is therefore inhibition of

FLJ14327 (Accession NM\_024912). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14327. FLJ23375 (Accession NM\_024956) is another VGAM638 host target gene. FLJ23375 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23375, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23375 BINDING SITE, designated SEQ ID:24513, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26665] Another function of VGAM638 is therefore inhibition of FLJ23375 (Accession NM\_024956). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23375. GTP Binding Protein 2 (GTPBP2, Accession NM\_019096) is another VGAM638 host target gene. GTPBP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GTPBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of GTPBP2 BINDING SITE, designated SEQ ID:21171, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26666] Another function of VGAM638 is therefore inhibition of GTP Binding Protein 2 (GTPBP2, Accession NM\_019096). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GTPBP2. KIAA0876 (Accession XM\_035625) is another VGAM638 host target gene. KIAA0876 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0876, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0876 BINDING SITE, designated SEQ ID:32295, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26667] Another function of VGAM638 is therefore inhibition of KIAA0876 (Accession XM\_035625). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0876. KIAA0923 (Accession NM\_014021) is another VGAM638 host target gene. KIAA0923 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0923 BINDING SITE, designated SEQ ID:15239, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26668] Another function of VGAM638 is therefore inhibition of KIAA0923 (Accession NM\_014021). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0923. Kelch-like 6 (Drosophila) (KLHL6, Accession NM\_130446) is another VGAM638 host target gene. KLHL6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KLHL6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KLHL6 BINDING SITE, designated SEQ ID:28211, to the nucleotide sequence of VGAM638 RNA,

herein designated VGAM RNA, also designated SEQ ID:3349.

[26669] Another function of VGAM638 is therefore inhibition of Kelch-like 6 (*Drosophila*) (KLHL6, Accession NM\_130446). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KLHL6. MDN1, Midasin Homolog (yeast) (MDN1, Accession XM\_031539) is another VGAM638 host target gene. MDN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MDN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MDN1 BINDING SITE, designated SEQ ID:31409, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26670] Another function of VGAM638 is therefore inhibition of MDN1, Midasin Homolog (yeast) (MDN1, Accession XM\_031539). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MDN1. MGC10870 (Accession NM\_032301) is another VGAM638 host target



gene. MGC10870 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGC10870, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC10870 BINDING SITE, designated SEQ ID:26080, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26671] Another function of VGAM638 is therefore inhibition of MGC10870 (Accession NM\_032301). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10870. MGC10981 (Accession NM\_032654) is another VGAM638 host target gene. MGC10981 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC10981, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC10981 BINDING SITE, designated SEQ ID:26387, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26672] Another function of VGAM638 is therefore inhibition of MGC10981 (Accession NM\_032654). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10981. RAB, Member of RAS Oncogene Family-like 4 (RABL4, Accession NM\_006860) is another VGAM638 host target gene. RABL4 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RABL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RABL4 BINDING SITE, designated SEQ ID:13730, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26673] Another function of VGAM638 is therefore inhibition of RAB, Member of RAS Oncogene Family-like 4 (RABL4, Accession NM\_006860). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RABL4. Signal-regulatory Protein Beta 1 (SIRPB1, Accession NM\_006065) is another VGAM638 host target gene. SIRPB1 BINDING SITE is HOST TARGET binding site found in the 3` un-

translated region of mRNA encoded by SIRPB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIRPB1 BINDING SITE, designated SEQ ID:12705, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26674] Another function of VGAM638 is therefore inhibition of Signal-regulatory Protein Beta 1 (SIRPB1, Accession NM\_006065). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIRPB1. Unc-5 Homolog D (C. elegans) (UNC5D, Accession NM\_080872) is another VGAM638 host target gene. UNC5D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UNC5D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UNC5D BINDING SITE, designated SEQ ID:28110, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26675] Another function of VGAM638 is therefore inhibition of

Unc-5 Homolog D (*C. elegans*) (UNC5D, Accession NM\_080872). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UNC5D. LOC150225 (Accession XM\_097870) is another VGAM638 host target gene. LOC150225 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150225, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150225 BINDING SITE, designated SEQ ID:41189, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26676] Another function of VGAM638 is therefore inhibition of LOC150225 (Accession XM\_097870). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150225. LOC154007 (Accession XM\_087824) is another VGAM638 host target gene. LOC154007 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154007, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154007 BINDING SITE, designated SEQ ID:39456, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26677] Another function of VGAM638 is therefore inhibition of LOC154007 (Accession XM\_087824). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154007. LOC154222 (Accession XM\_098497) is another VGAM638 host target gene. LOC154222 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154222, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154222 BINDING SITE, designated SEQ ID:41692, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26678] Another function of VGAM638 is therefore inhibition of LOC154222 (Accession XM\_098497). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC154222. LOC157918 (Accession XM\_098842) is another VGAM638 host target gene. LOC157918 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157918, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157918 BINDING SITE, designated SEQ ID:41894, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26679] Another function of VGAM638 is therefore inhibition of LOC157918 (Accession XM\_098842). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157918. LOC157919 (Accession XM\_088420) is another VGAM638 host target gene. LOC157919 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157919, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157919 BINDING SITE, designated SEQ ID:39681, to the nucleotide sequence of VGAM638 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3349.

[26680] Another function of VGAM638 is therefore inhibition of LOC157919 (Accession XM\_088420). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157919. LOC201562 (Accession XM\_114343) is another VGAM638 host target gene. LOC201562 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201562, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201562 BINDING SITE, designated SEQ ID:42884, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26681] Another function of VGAM638 is therefore inhibition of LOC201562 (Accession XM\_114343). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201562. LOC257106 (Accession XM\_170910) is another VGAM638 host target gene. LOC257106 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257106, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257106 BINDING SITE, designated SEQ ID:45676, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26682] Another function of VGAM638 is therefore inhibition of LOC257106 (Accession XM\_170910). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257106. LOC92689 (Accession XM\_046663) is another VGAM638 host target gene. LOC92689 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92689, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92689 BINDING SITE, designated SEQ ID:34783, to the nucleotide sequence of VGAM638 RNA, herein designated VGAM RNA, also designated SEQ ID:3349.

[26683] Another function of VGAM638 is therefore inhibition of LOC92689 (Accession XM\_046663). Accordingly, utilities of VGAM638 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with LOC92689. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 639 (VGAM639) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26684] VGAM639 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM639 was detected is described hereinabove with reference to Figs. 1–8.

[26685] VGAM639 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turnip Mosaic Virus. VGAM639 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26686] VGAM639 gene encodes a VGAM639 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM639 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM639 precursor RNA is designated SEQ

ID:625, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:625 is located at position 5030 relative to the genome of Turnip Mosaic Virus.

[26687] VGAM639 precursor RNA folds onto itself, forming VGAM639 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26688] An enzyme complex designated DICER COMPLEX, `dices` the VGAM639 folded precursor RNA into VGAM639 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM639 RNA is designated SEQ ID:3350, and is provided hereinbelow with reference to the sequence

listing part.

[26689] VGAM639 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM639 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM639 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26690] VGAM639 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM639 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM639 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM639 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM639 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26691] The complementary binding of VGAM639 RNA, herein designated VGAM RNA, to host target binding sites on VGAM639 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM639 host target RNA into VGAM639 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26692] It is appreciated that VGAM639 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM639 host target genes. The mRNA of each one of this plurality of VGAM639 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM639 RNA, herein designated VGAM

RNA, and which when bound by VGAM639 RNA causes inhibition of translation of respective one or more VGAM639 host target proteins.

[26693] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM639 gene, herein designated VGAM GENE, on one or more VGAM639 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26694] It is yet further appreciated that a function of VGAM639 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM639 include diagnosis, prevention and treatment of viral infection by Turnip Mosaic Virus. Specific functions, and accordingly utilities, of VGAM639 correlate with, and may be deduced from, the identity of the host target genes which VGAM639 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26695] Nucleotide sequences of the VGAM639 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM639 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM639 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM639 are further described hereinbelow with reference to Table 1.

[26696] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM639 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM639 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26697] As mentioned hereinabove with reference to Fig. 1, a function of VGAM639 gene, herein designated VGAM is

inhibition of expression of VGAM639 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM639 correlate with, and may be deduced from, the identity of the target genes which VGAM639 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26698] GLI-Kruppel Family Member GLI2 (GLI2, Accession NM\_030379) is a VGAM639 host target gene. GLI2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GLI2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLI2 BINDING SITE, designated SEQ ID:24938, to the nucleotide sequence of VGAM639 RNA, herein designated VGAM RNA, also designated SEQ ID:3350.

[26699] A function of VGAM639 is therefore inhibition of GLI-Kruppel Family Member GLI2 (GLI2, Accession NM\_030379), a gene which may promote tax-dependent transcription of T-cell leukemia virus type 1 genes. Accordingly, utilities of VGAM639 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLI2. The function of GLI2 and its associa-

tion with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM465. Chromosome 11 Open Reading Frame 23 (C11orf23, Accession NM\_018312) is another VGAM639 host target gene. C11orf23 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C11orf23, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C11orf23 BINDING SITE, designated SEQ ID:20303, to the nucleotide sequence of VGAM639 RNA, herein designated VGAM RNA, also designated SEQ ID:3350.

[26700] Another function of VGAM639 is therefore inhibition of Chromosome 11 Open Reading Frame 23 (C11orf23, Accession NM\_018312). Accordingly, utilities of VGAM639 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C11orf23. ECE2 (Accession NM\_014693) is another VGAM639 host target gene. ECE2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ECE2, corresponding to a HOST TARGET binding site such



as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ECE2 BINDING SITE, designated SEQ ID:16198, to the nucleotide sequence of VGAM639 RNA, herein designated VGAM RNA, also designated SEQ ID:3350.

[26701] Another function of VGAM639 is therefore inhibition of ECE2 (Accession NM\_014693). Accordingly, utilities of VGAM639 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ECE2. FLJ10901 (Accession NM\_018265) is another VGAM639 host target gene. FLJ10901 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10901, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10901 BINDING SITE, designated SEQ ID:20230, to the nucleotide sequence of VGAM639 RNA, herein designated VGAM RNA, also designated SEQ ID:3350.

[26702] Another function of VGAM639 is therefore inhibition of FLJ10901 (Accession NM\_018265). Accordingly, utilities of VGAM639 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10901.

Zinc Finger Protein 317 (ZNF317, Accession XM\_050435) is another VGAM639 host target gene. ZNF317 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF317 BINDING SITE, designated SEQ ID:35636, to the nucleotide sequence of VGAM639 RNA, herein designated VGAM RNA, also designated SEQ ID:3350.

[26703] Another function of VGAM639 is therefore inhibition of Zinc Finger Protein 317 (ZNF317, Accession XM\_050435). Accordingly, utilities of VGAM639 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF317. LOC245771 (Accession XM\_167366) is another VGAM639 host target gene. LOC245771 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC245771, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC245771 BINDING SITE, designated SEQ ID:44635, to the nucleotide sequence of

VGAM639 RNA, herein designated VGAM RNA, also designated SEQ ID:3350.

[26704] Another function of VGAM639 is therefore inhibition of LOC245771 (Accession XM\_167366). Accordingly, utilities of VGAM639 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC245771. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 640 (VGAM640) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26705] VGAM640 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM640 was detected is described hereinabove with reference to Figs. 1–8.

[26706] VGAM640 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turnip Mosaic Virus. VGAM640 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26707] VGAM640 gene encodes a VGAM640 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM640 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM640 precursor RNA is designated SEQ ID:626, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:626 is located at position 9395 relative to the genome of Turnip Mosaic Virus.

[26708] VGAM640 precursor RNA folds onto itself, forming VGAM640 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26709] An enzyme complex designated DICER COMPLEX, `dices` the VGAM640 folded precursor RNA into VGAM640 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM640 RNA is designated SEQ ID:3351, and is provided hereinbelow with reference to the sequence listing part.

[26710] VGAM640 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM640 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM640 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[26711] VGAM640 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM640 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM640 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM640 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM640 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26712] The complementary binding of VGAM640 RNA, herein designated VGAM RNA, to host target binding sites on VGAM640 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM640 host target RNA into VGAM640 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26713] It is appreciated that VGAM640 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM640 host target genes. The mRNA of each one of this plurality of VGAM640 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM640 RNA, herein designated VGAM RNA, and which when bound by VGAM640 RNA causes inhibition of translation of respective one or more VGAM640 host target proteins.

[26714] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM640 gene, herein designated VGAM GENE, on one or more VGAM640 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[26715] It is yet further appreciated that a function of VGAM640 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of viral infection by Turnip Mosaic Virus. Specific functions, and accordingly utilities, of VGAM640 correlate with, and may be deduced from, the identity of the host target genes which VGAM640 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26716] Nucleotide sequences of the VGAM640 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM640 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM640 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM640 are further described hereinbelow with reference to Table 1.

[26717] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM640 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM640 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26718] As mentioned hereinabove with reference to Fig. 1, a function of VGAM640 gene, herein designated VGAM is inhibition of expression of VGAM640 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM640 correlate with, and may be deduced from, the identity of the target genes which VGAM640 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26719] G Protein-coupled Receptor Kinase 7 (GPRK7, Accession NM\_139209) is a VGAM640 host target gene. GPRK7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPRK7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPRK7 BINDING SITE, designated SEQ ID:29228, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26720] A function of VGAM640 is therefore inhibition of G Protein-coupled Receptor Kinase 7 (GPRK7, Accession

NM\_139209), a gene which may play a role in signal transduction pathways that involve calcium as a second messenger. Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPRK7. The function of GPRK7 has been established by previous studies. Weiss et al. (2001) cloned GRK7 from a human retina cDNA library using primers designed from the pig GRK7 sequence. GRK7 encodes a deduced 553-amino acid protein with a calculated molecular mass of 62 kD. The protein contains a CaaX motif for isoprenylation and carboxymethylation of the C terminus, an autophosphorylation site at ser491, and a motif for geranylgeranylation. GRK7 shares 85% and 59% amino acid identity with the pig and medaka fish GRK7, respectively, and 47% identity with GRK1 (OMIM Ref. No. 180381). Western blot analysis revealed an apparent molecular mass of 62 kD for purified recombinant human GRK7, and an identical mass in retinal extracts of various mammalian species. Immunolocalization using human retina sections showed staining limited to cone cells, with particularly intense staining in the outer segments. Weiss et al. (2001) noted that GRK1 is expressed in both cones and rods. By database analysis, Chen et al.

(2001) independently identified GRK7 and cloned GRK7 from a human retinal cDNA library and from human retinal mRNA by PCR and RT-PCR. RT-PCR revealed retina-specific expression in human tissues. Western blot analysis detected a 64-kD band in human retina, but not in any of the other 11 tissues tested. Immunocytochemistry showed positive staining for GRK7 in the nuclear layers, the inner and outer plexiform layers, and the inner segment layer. GRK7 colocalized with GRK1 in human cone outer segments. In retina from a 4-month-old donor, GRK7 was specifically localized to the proximal portion of the cone outer segments. Western blot analysis of mouse tissues showed more widespread expression, including not only retina but brain, olfactory bulb, lung, and pancreas. In the mouse retina, staining was seen in the inner and outer plexiform layers and in the nucleus of the inner nuclear and ganglion cell layers. Outer segment layers were negative for Grk7.

[26721] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26722] Chen, C.-K.; Zhang, K.; Church-Kopish, J.; Huang, W.; Zhang, H.; Chen, Y.-J.; Frederick, J. M.; Baehr, W. : Charac-

terization of human GRK7 as a potential cone opsin kinase. *Molec. Vision* 7: 305–313, 2001. ; and

[26723] Weiss, E. R.; Ducceschi, M. H.; Horner, T. J.; Li, A.; Craft, C. M.; Osawa, S. : Species-specific differences in expression of G-protein-coupled receptor kinase (GRK) 7 and GRK1 in mam.

[26724] Further studies establishing the function and utilities of GPRK7 are found in John Hopkins OMIM database record ID 606987, and in cited publications numbered 5529–5530 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Integrin, Alpha L (antigen CD11A (p180), Lymphocyte Function-associated Antigen 1; Alpha Polypeptide) (ITGAL, Accession NM\_002209) is another VGAM640 host target gene. ITGAL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGAL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGAL BINDING SITE, designated SEQ ID:7971, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26725] Another function of VGAM640 is therefore inhibition of

Integrin, Alpha L (antigen CD11A (p180), Lymphocyte Function-associated Antigen 1; Alpha Polypeptide) (ITGAL, Accession NM\_002209), a gene which is a receptor for icam1, icam2, icam3 and icam4. It is involved in a variety of immune phenomena including leukocyte-endothelial cell interaction, cytotoxic t-cell mediated killing, and antibody dependent killing by granulocytes and monocytes. Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGAL. The function of ITGAL and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM200.

Integrin, Beta 3 (platelet glycoprotein IIIa, antigen CD61) (ITGB3, Accession NM\_000212) is another VGAM640 host target gene. ITGB3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGB3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGB3 BINDING SITE, designated SEQ ID:5707, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26726] Another function of VGAM640 is therefore inhibition of Integrin, Beta 3 (platelet glycoprotein IIIa, antigen CD61) (ITGB3, Accession NM\_000212). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGB3. V-myc Myelocytomatosis Viral Oncogene Homolog 1, Lung Carcinoma Derived (avian) (MYCL1, Accession NM\_005376) is another VGAM640 host target gene. MYCL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYCL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYCL1 BINDING SITE, designated SEQ ID:11853, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26727] Another function of VGAM640 is therefore inhibition of V-myc Myelocytomatosis Viral Oncogene Homolog 1, Lung Carcinoma Derived (avian) (MYCL1, Accession NM\_005376), a gene which is a Myc-like transcription factor. Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical con-

ditions associated with MYCL1. The function of MYCL1 has been established by previous studies. Nau et al. (1985) cloned from DNA of small-cell lung cancer (SCCL) a gene with homology to a small region of both MYC (OMIM Ref. No. 190080) and NMYC (OMIM Ref. No. 164840). By somatic cell hybridization and in situ hybridization, they assigned the gene to 1p32. This LMYC sequence was amplified 10- to 20-fold in the DNA of 4 SCCL lines and of 1 SCCL specimen taken directly from a patient. A restriction polymorphism was found. In heterozygotes, only 1 of the 2 alleles was amplified in any 1 genome. In a linkage map of chromosome 1 prepared by Rouleau et al. (1990), it was concluded that MYCL1 is 17 cM proximal to RH. Kaye et al. (1988) found that the LMYC gene is composed of 3 exons and 2 introns spanning 6.6 kilobases. Several distinct mRNAs were produced in all SCCL cell lines that expressed LMYC. These transcripts were generated from a single gene by alternative splicing of introns 1 and 2 and by use of alternative polyadenylation signals. Comparisons with MYC and NMYC demonstrated multiple discrete regions with extensive homology. Kawashima et al. (1988) concluded that a correlation exists between particular RFLP alleles of the MYCL gene and the occurrence of

metastasis of lung cancer to lymph nodes and other organs. Among lung cancer patients, those with only the L band (10 kb) had few lymph node metastases, whereas patients with either the S band (6 kb) or the S and L bands almost always had lymph node metastases. A similar correlation was found between the presence of the S band and metastases to other organs. The correlation was particularly marked in cases of adenocarcinoma of the lung. By study of DNA from mouse–hamster somatic cell hybrids, Campbell et al. (1989) mapped 2 L–myc loci provisionally to mouse chromosomes 4 and 12. The locus on chromosome 12 may be a pseudogene. When studying chromosome 1p breakpoints in neuroblastoma cell lines using fluorescence in situ hybridization (FISH) with region–specific probes, Van Roy et al. (1995) found evidence for a position of MYCL1 more distal than 1p32. To investigate the discrepancy Speleman et al. (1996) used FISH on high–resolution R–banded chromosomes with a YAC clone for MYCL1 and reassigned the gene to 1p34.3.

[26728] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26729] Kawashima, K.; Shikama, H.; Imoto, K.; Izawa, M.; Naruke,



T.; Okabayashi, K.; Nishimura, S. : Close correlation between restriction fragment length polymorphism of the L-MYC gene and metastasis of human lung cancer to the lymph nodes and other organs. Proc. Nat. Acad. Sci. 85: 2353–2356, 1988. ; and

[26730] Kaye, F.; Battey, J.; Nau, M.; Brooks, B.; Seifter, E.; De Greve, J.; Birrer, M.; Sausville, E.; Minna, J. : Structure and expression of the human L-myc gene reveal a complex pattern of.

[26731] Further studies establishing the function and utilities of MYCL1 are found in John Hopkins OMIM database record ID 164850, and in cited publications numbered 173 and 1818–1824 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Sirtuin Silent Mating Type Information Regulation 2 Homolog 2 (*S. cerevisiae*) (SIRT2, Accession NM\_030593) is another VGAM640 host target gene. SIRT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIRT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIRT2 BINDING SITE, designated SEQ ID:24958, to the nucleotide sequence of

VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26732] Another function of VGAM640 is therefore inhibition of Sirtuin Silent Mating Type Information Regulation 2 Homolog 2 (*S. cerevisiae*) (SIRT2, Accession NM\_030593), a gene which might function in telomeric silencing, cell cycle progression and chromosome stability. Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIRT2. The function of SIRT2 has been established by previous studies. The yeast Sir2 protein (Shore et al., 1984) regulates epigenetic gene silencing and, as a possible antiaging effect, suppresses recombination of rDNA. Studies involving cobB, a bacterial Sir2-like gene, have suggested that Sir2 may encode a pyridine nucleotide transferase. By in silico and PCR-cloning techniques, Frye (1999) obtained cDNA sequences encoding 5 human Sir2-like genes, which they called sirtuin-1 to -5 (SIRT1 to SIRT5). The SIRT1 (OMIM Ref. No. 604479) sequence has the closest homology to the *S. cerevisiae* Sir2 protein, while SIRT4 (OMIM Ref. No. 604482) and SIRT5 (OMIM Ref. No. 604483) more closely resemble prokaryotic sirtuin sequences. PCR analysis showed that the 5 human sirtuins

are widely expressed in fetal and adult tissues. Recombinant human SIRT2 was able to cause radioactivity to be transferred from (32P)NAD to bovine serum albumin (BSA). When a conserved histidine within SIRT2 was converted to tyrosine, the mutant recombinant protein was unable to transfer radioactivity from (32P)NAD to BSA. These results suggested that the sirtuins may function via mono-ADP-ribosylation of proteins. Tanny et al. (1999) showed that the yeast Sir2 protein can transfer labeled phosphate from nicotinamide adenine dinucleotide to itself and histones in vitro. A modified form of Sir2, which results from its automodification activity, was specifically recognized by anti-mono-ADP-ribose antibodies, suggesting that Sir2 is an ADP-ribosyltransferase. Mutation of a phylogenetically invariant histidine (his364 to tyr) in Sir2 abolished both its enzymatic activity in vitro and its silencing functions in vivo. However, the mutant protein was associated with chromatin and other silencing factors in a manner similar to wildtype Sir2. These findings suggested that Sir2 contains an ADP-ribosyltransferase activity that is essential for its silencing function.

[26733] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [26734] Frye, R. A. : Characterization of five human cDNAs with homology to the yeast SIR2 gene: Sir2-like proteins (sirtuins) metabolize NAD and may have protein ADP-ribosyltransferase activity. *Biochem. Biophys. Res. Commun.* 260: 273–279, 1999. ; and
- [26735] Tanny, J. C.; Dowd, G. J.; Huang, J.; Hilz, H.; Moazed, D. : An enzymatic activity in the yeast Sir2 protein that is essential for gene silencing. *Cell* 99: 735–745, 1999.
- [26736] Further studies establishing the function and utilities of SIRT2 are found in John Hopkins OMIM database record ID 604480, and in cited publications numbered 5008, 504 and 5051 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tumor Protein D52-like 2 (TPD52L2, Accession NM\_003288) is another VGAM640 host target gene. TPD52L2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TPD52L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TPD52L2 BINDING SITE, designated SEQ ID:9297, to the nucleotide sequence of VGAM640 RNA, herein designated

VGAM RNA, also designated SEQ ID:3351.

[26737] Another function of VGAM640 is therefore inhibition of Tumor Protein D52-like 2 (TPD52L2, Accession NM\_003288). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TPD52L2. Zinc Finger Protein 261 (ZNF261, Accession NM\_005096) is another VGAM640 host target gene. ZNF261 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF261 BINDING SITE, designated SEQ ID:11563, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26738] Another function of VGAM640 is therefore inhibition of Zinc Finger Protein 261 (ZNF261, Accession NM\_005096). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF261. Chromosome 20 Open Reading Frame 103 (C20orf103, Accession NM\_012261) is another VGAM640 host target gene. C20orf103 BINDING SITE is

HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by C20orf103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf103 BINDING SITE, designated SEQ ID:14570, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26739] Another function of VGAM640 is therefore inhibition of Chromosome 20 Open Reading Frame 103 (C20orf103, Accession NM\_012261). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf103. MGC5242 (Accession NM\_024033) is another VGAM640 host target gene. MGC5242 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC5242, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5242 BINDING SITE, designated SEQ ID:23464, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26740] Another function of VGAM640 is therefore inhibition of MGC5242 (Accession NM\_024033). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5242. Sema Domain, Immunoglobulin Domain (Ig), Short Basic Domain, Secreted, (semaphorin) 3E (SEMA3E, Accession NM\_012431) is another VGAM640 host target gene. SEMA3E BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SEMA3E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA3E BINDING SITE, designated SEQ ID:14809, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26741] Another function of VGAM640 is therefore inhibition of Sema Domain, Immunoglobulin Domain (Ig), Short Basic Domain, Secreted, (semaphorin) 3E (SEMA3E, Accession NM\_012431). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA3E. LOC112817 (Accession NM\_138413) is another VGAM640 host target

gene. LOC112817 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC112817, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112817 BINDING SITE, designated SEQ ID:28781, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26742] Another function of VGAM640 is therefore inhibition of LOC112817 (Accession NM\_138413). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112817. LOC147353 (Accession XM\_097227) is another VGAM640 host target gene. LOC147353 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC147353, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147353 BINDING SITE, designated SEQ ID:40834, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.



[26743] Another function of VGAM640 is therefore inhibition of LOC147353 (Accession XM\_097227). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147353. LOC63923 (Accession XM\_040527) is another VGAM640 host target gene. LOC63923 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC63923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC63923 BINDING SITE, designated SEQ ID:33325, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26744] Another function of VGAM640 is therefore inhibition of LOC63923 (Accession XM\_040527). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC63923. LOC91301 (Accession XM\_037564) is another VGAM640 host target gene. LOC91301 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC91301, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91301 BINDING SITE, designated SEQ ID:32647, to the nucleotide sequence of VGAM640 RNA, herein designated VGAM RNA, also designated SEQ ID:3351.

[26745] Another function of VGAM640 is therefore inhibition of LOC91301 (Accession XM\_037564). Accordingly, utilities of VGAM640 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91301. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 641 (VGAM641) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26746] VGAM641 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM641 was detected is described hereinabove with reference to Figs. 1–8.

[26747] VGAM641 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rat Cytomegalovirus. VGAM641 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[26748] VGAM641 gene encodes a VGAM641 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM641 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM641 precursor RNA is designated SEQ ID:627, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:627 is located at position 50326 relative to the genome of Rat Cytomegalovirus.

[26749] VGAM641 precursor RNA folds onto itself, forming VGAM641 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26750] An enzyme complex designated DICER COMPLEX, `dices` the VGAM641 folded precursor RNA into VGAM641 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM641 RNA is designated SEQ ID:3352, and is provided hereinbelow with reference to the sequence listing part.

[26751] VGAM641 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM641 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM641 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26752] VGAM641 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM641 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM641 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM641 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM641 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26753] The complementary binding of VGAM641 RNA, herein designated VGAM RNA, to host target binding sites on VGAM641 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM641 host target RNA into VGAM641 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[26754] It is appreciated that VGAM641 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM641 host target genes. The mRNA of each one of this plurality of VGAM641 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM641 RNA, herein designated VGAM RNA, and which when bound by VGAM641 RNA causes inhibition of translation of respective one or more VGAM641 host target proteins.

[26755] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM641 gene, herein designated VGAM GENE, on one or more VGAM641 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26756] It is yet further appreciated that a function of VGAM641 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM641 include diagnosis, prevention and treatment of viral infection by Rat Cytomegalovirus. Specific functions, and accordingly utilities, of VGAM641 correlate with, and may be deduced from, the identity of the host target genes which VGAM641 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26757] Nucleotide sequences of the VGAM641 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM641 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM641 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM641 are further described hereinbelow with reference to Table 1.

[26758] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM641 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM641 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26759] As mentioned hereinabove with reference to Fig. 1, a function of VGAM641 gene, herein designated VGAM is inhibition of expression of VGAM641 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM641 correlate with, and may be deduced from, the identity of the target genes which VGAM641 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26760] Polycystic Kidney Disease (polycystin) and REJ (sperm receptor for egg jelly homolog, sea urchin)-like (PKDREJ, Accession NM\_006071) is a VGAM641 host target gene. PKDREJ BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PKDREJ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PKDREJ BINDING SITE, designated SEQ



ID:12714, to the nucleotide sequence of VGAM641 RNA, herein designated VGAM RNA, also designated SEQ ID:3352.

[26761] A function of VGAM641 is therefore inhibition of Polycystic Kidney Disease (polycystin) and REJ (sperm receptor for egg jelly homolog, sea urchin)-like (PKDREJ, Accession NM\_006071), a gene which may intervene in fertilization. Accordingly, utilities of VGAM641 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PKDREJ. The function of PKDREJ has been established by previous studies. By searching cDNA and genomic databases for sequences similar to PKD1 (OMIM Ref. No. 601313), PKD2 (OMIM Ref. No. 173910), and the sea urchin sperm receptor for egg jelly (suREJ), Hughes et al. (1999) identified an intronless gene, which they designated PKDREJ, on cosmids located on chromosome 22q13. By screening a testis cDNA library, the authors obtained a PKDREJ cDNA encoding a deduced 2,253-amino acid protein. The PKDREJ protein is 64% identical and 78% similar to the mouse Pkdrej protein. Hydrophobicity analysis indicated that the structure of PKDREJ, with 11 transmembrane regions, is similar to that of PKD1. Northern blot analysis showed expression of an approximately 8-kb

PKDREJ transcript exclusively in testis, coincident with the timing of sperm maturation. By radiation hybrid analysis, Veldhuisen et al. (1999) mapped the PKDREJ gene to chromosome 22q13.3.

[26762] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26763] Hughes, J.; Ward, C. J.; Aspinwall, R.; Butler, R.; Harris, P. C. : Identification of a human homologue of the sea urchin receptor for egg jelly: a polycystic kidney disease-like protein. Hum. Molec. Genet. 8: 543–549, 1999. ; and

[26764] Veldhuisen, B.; Spruit, L.; Dauwerse, H. G.; Breuning, M. H.; Peters, D. J. : Genes homologous to the autosomal dominant polycystic kidney disease genes (PKD1 and PKD2). Europ. J. Hum.

[26765] Further studies establishing the function and utilities of PKDREJ are found in John Hopkins OMIM database record ID 604670, and in cited publications numbered 7483 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chloride Intracellular Channel 5 (CLIC5, Accession NM\_016929) is another VGAM641 host target gene. CLIC5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region

of mRNA encoded by CLIC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLIC5 BINDING SITE, designated SEQ ID:18847, to the nucleotide sequence of VGAM641 RNA, herein designated VGAM RNA, also designated SEQ ID:3352.

[26766] Another function of VGAM641 is therefore inhibition of Chloride Intracellular Channel 5 (CLIC5, Accession NM\_016929). Accordingly, utilities of VGAM641 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLIC5. FLJ23360 (Accession NM\_023076) is another VGAM641 host target gene. FLJ23360 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ23360, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23360 BINDING SITE, designated SEQ ID:23334, to the nucleotide sequence of VGAM641 RNA, herein designated VGAM RNA, also designated SEQ ID:3352.

[26767] Another function of VGAM641 is therefore inhibition of

FLJ23360 (Accession NM\_023076). Accordingly, utilities of VGAM641 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23360. RTP801 (Accession NM\_019058) is another VGAM641 host target gene. RTP801 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RTP801, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RTP801 BINDING SITE, designated SEQ ID:21141, to the nucleotide sequence of VGAM641 RNA, herein designated VGAM RNA, also designated SEQ ID:3352.

[26768] Another function of VGAM641 is therefore inhibition of RTP801 (Accession NM\_019058). Accordingly, utilities of VGAM641 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RTP801. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 642 (VGAM642) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26769] VGAM642 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM642 was detected is described hereinabove with reference to Figs. 1–8.

[26770] VGAM642 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rat Cytomegalovirus. VGAM642 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26771] VGAM642 gene encodes a VGAM642 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM642 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM642 precursor RNA is designated SEQ ID:628, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:628 is located at position 96235 relative to the genome of Rat Cytomegalovirus.

[26772] VGAM642 precursor RNA folds onto itself, forming VGAM642 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26773] An enzyme complex designated DICER COMPLEX, `dices` the VGAM642 folded precursor RNA into VGAM642 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM642 RNA is designated SEQ ID:3353, and is provided hereinbelow with reference to the sequence listing part.

[26774] VGAM642 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM642 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM642 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[26775] VGAM642 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM642 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM642 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM642 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM642 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26776] The complementary binding of VGAM642 RNA, herein designated VGAM RNA, to host target binding sites on VGAM642 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM642 host target RNA into VGAM642 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26777] It is appreciated that VGAM642 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM642 host target genes. The mRNA of each one of this plurality of VGAM642 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM642 RNA, herein designated VGAM RNA, and which when bound by VGAM642 RNA causes inhibition of translation of respective one or more VGAM642 host target proteins.

[26778] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM642 gene, herein designated VGAM GENE, on one or more VGAM642 host target gene, herein designated



VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26779] It is yet further appreciated that a function of VGAM642 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM642 include diagnosis, prevention and treatment of viral infection by Rat Cytomegalovirus. Specific functions, and accordingly utilities, of VGAM642 correlate with, and may be deduced from, the identity of the host target genes which VGAM642 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26780] Nucleotide sequences of the VGAM642 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM642 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM642 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM642 are further  
described hereinbelow with reference to Table 1.

[26781] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM642 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM642 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[26782] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM642 gene, herein designated VGAM is  
inhibition of expression of VGAM642 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM642 correlate with, and may be deduced  
from, the identity of the target genes which VGAM642  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[26783] ATPase, Cu++ Transporting, Beta Polypeptide (Wilson dis-  
ease) (ATP7B, Accession NM\_000053) is a VGAM642 host

target gene. ATP7B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP7B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP7B BINDING SITE, designated SEQ ID:5502, to the nucleotide sequence of VGAM642 RNA, herein designated VGAM RNA, also designated SEQ ID:3353.

[26784] A function of VGAM642 is therefore inhibition of ATPase, Cu++ Transporting, Beta Polypeptide (Wilson disease) (ATP7B, Accession NM\_000053). Accordingly, utilities of VGAM642 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP7B.

Beta-1,3-glucuronyltransferase 1

(glucuronosyltransferase P) (B3GAT1, Accession NM\_018644) is another VGAM642 host target gene.

B3GAT1 BINDING SITE1 and B3GAT1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by B3GAT1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B3GAT1 BINDING

SITE1 and B3GAT1 BINDING SITE2, designated SEQ ID:20718 and SEQ ID:27630 respectively, to the nucleotide sequence of VGAM642 RNA, herein designated VGAM RNA, also designated SEQ ID:3353.

[26785] Another function of VGAM642 is therefore inhibition of Beta-1,3-glucuronyltransferase 1 (glucuronosyltransferase P) (B3GAT1, Accession NM\_018644). Accordingly, utilities of VGAM642 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B3GAT1. EGF-like-domain, Multiple 3 (EGFL3, Accession XM\_031401) is another VGAM642 host target gene. EGFL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGFL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGFL3 BINDING SITE, designated SEQ ID:31373, to the nucleotide sequence of VGAM642 RNA, herein designated VGAM RNA, also designated SEQ ID:3353.

[26786] Another function of VGAM642 is therefore inhibition of EGF-like-domain, Multiple 3 (EGFL3, Accession XM\_031401). Accordingly, utilities of VGAM642 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with EGFL3. KIAA0513 (Accession NM\_014732) is another VGAM642 host target gene. KIAA0513 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0513, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0513 BINDING SITE, designated SEQ ID:16355, to the nucleotide sequence of VGAM642 RNA, herein designated VGAM RNA, also designated SEQ ID:3353.

[26787] Another function of VGAM642 is therefore inhibition of KIAA0513 (Accession NM\_014732). Accordingly, utilities of VGAM642 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0513. LOC149478 (Accession XM\_086536) is another VGAM642 host target gene. LOC149478 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149478, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC149478 BINDING SITE, designated SEQ ID:38754, to the nucleotide sequence of VGAM642 RNA, herein designated VGAM RNA, also designated SEQ ID:3353.

[26788] Another function of VGAM642 is therefore inhibition of LOC149478 (Accession XM\_086536). Accordingly, utilities of VGAM642 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149478. LOC203378 (Accession XM\_117541) is another VGAM642 host target gene. LOC203378 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC203378, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203378 BINDING SITE, designated SEQ ID:43554, to the nucleotide sequence of VGAM642 RNA, herein designated VGAM RNA, also designated SEQ ID:3353.

[26789] Another function of VGAM642 is therefore inhibition of LOC203378 (Accession XM\_117541). Accordingly, utilities of VGAM642 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203378. LOC91179 (Accession XM\_036731) is another VGAM642 host target gene. LOC91179 BINDING

SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91179, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91179 BINDING SITE, designated SEQ ID:32492, to the nucleotide sequence of VGAM642 RNA, herein designated VGAM RNA, also designated SEQ ID:3353.

[26790] Another function of VGAM642 is therefore inhibition of LOC91179 (Accession XM\_036731). Accordingly, utilities of VGAM642 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91179. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 643 (VGAM643) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26791] VGAM643 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM643 was detected is described hereinabove with reference to Figs. 1-8.

[26792] VGAM643 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rat Cytomegalovirus. VGAM643 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26793] VGAM643 gene encodes a VGAM643 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM643 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM643 precursor RNA is designated SEQ ID:629, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:629 is located at position 112209 relative to the genome of Rat Cytomegalovirus.

[26794] VGAM643 precursor RNA folds onto itself, forming VGAM643 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-



cleotide sequence of the second half thereof.

[26795] An enzyme complex designated DICER COMPLEX, `dices` the VGAM643 folded precursor RNA into VGAM643 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM643 RNA is designated SEQ ID:3354, and is provided hereinbelow with reference to the sequence listing part.

[26796] VGAM643 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM643 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM643 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26797] VGAM643 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM643 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM643 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM643 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM643 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[26798] The complementary binding of VGAM643 RNA, herein designated VGAM RNA, to host target binding sites on VGAM643 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM643 host target RNA into VGAM643 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26799] It is appreciated that VGAM643 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM643 host target genes. The mRNA of each one of this plurality of VGAM643 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM643 RNA, herein designated VGAM RNA, and which when bound by VGAM643 RNA causes inhibition of translation of respective one or more VGAM643 host target proteins.

[26800] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM643 gene, herein designated VGAM GENE, on one or more VGAM643 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26801] It is yet further appreciated that a function of VGAM643 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of viral infection by Rat Cytomegalovirus. Specific functions, and accordingly utilities, of VGAM643 correlate with, and may be deduced from, the identity of the host target genes which VGAM643 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26802] Nucleotide sequences of the VGAM643 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM643 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM643 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM643 are further described hereinbelow with reference to Table 1.

[26803] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM643 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM643 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26804] As mentioned hereinabove with reference to Fig. 1, a function of VGAM643 gene, herein designated VGAM is inhibition of expression of VGAM643 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM643 correlate with, and may be deduced from, the identity of the target genes which VGAM643 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26805] SMURF1 (Accession XM\_166483) is a VGAM643 host target gene. SMURF1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SMURF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of SMURF1 BINDING SITE, designated SEQ ID:44411, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26806] A function of VGAM643 is therefore inhibition of SMURF1 (Accession XM\_166483). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMURF1. FLJ12443 (Accession NM\_024830) is another VGAM643 host target gene. FLJ12443 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12443, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12443 BINDING SITE, designated SEQ ID:24225, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26807] Another function of VGAM643 is therefore inhibition of FLJ12443 (Accession NM\_024830). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12443. KIAA0229 (Accession XM\_166478) is another VGAM643

host target gene. KIAA0229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0229 BINDING SITE, designated SEQ ID:44401, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26808] Another function of VGAM643 is therefore inhibition of KIAA0229 (Accession XM\_166478). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0229. KIAA0674 (Accession XM\_027054) is another VGAM643 host target gene. KIAA0674 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0674, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0674 BINDING SITE, designated SEQ ID:30399, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26809] Another function of VGAM643 is therefore inhibition of KIAA0674 (Accession XM\_027054). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0674. KIAA0712 (Accession NM\_014715) is another VGAM643 host target gene. KIAA0712 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0712, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0712 BINDING SITE, designated SEQ ID:16264, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26810] Another function of VGAM643 is therefore inhibition of KIAA0712 (Accession NM\_014715). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0712. KIAA1229 (Accession XM\_030665) is another VGAM643 host target gene. KIAA1229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1229, corresponding to a HOST TARGET binding site such as BINDING SITE I,



BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1229 BINDING SITE, designated SEQ ID:31100, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26811] Another function of VGAM643 is therefore inhibition of KIAA1229 (Accession XM\_030665). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1229. Ring Finger Protein 10 (RNF10, Accession NM\_014868) is another VGAM643 host target gene. RNF10 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RNF10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF10 BINDING SITE, designated SEQ ID:16963, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26812] Another function of VGAM643 is therefore inhibition of Ring Finger Protein 10 (RNF10, Accession NM\_014868). Accordingly, utilities of VGAM643 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with RNF10. Serologically Defined Colon Cancer Antigen 43 (SDCCAG43, Accession XM\_046834) is another VGAM643 host target gene. SDCCAG43 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDCCAG43, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDCCAG43 BINDING SITE, designated SEQ ID:34845, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26813] Another function of VGAM643 is therefore inhibition of Serologically Defined Colon Cancer Antigen 43 (SDCCAG43, Accession XM\_046834). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDCCAG43. SMOC2 (Accession XM\_051452) is another VGAM643 host target gene. SMOC2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SMOC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of SMOC2 BINDING SITE, designated SEQ ID:35835, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26814] Another function of VGAM643 is therefore inhibition of SMOC2 (Accession XM\_051452). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMOC2. Stromal Antigen 2 (STAG2, Accession XM\_047285) is another VGAM643 host target gene. STAG2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by STAG2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAG2 BINDING SITE, designated SEQ ID:34931, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26815] Another function of VGAM643 is therefore inhibition of Stromal Antigen 2 (STAG2, Accession XM\_047285). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAG2. LOC253981 (Accession XM\_171064)

is another VGAM643 host target gene. LOC253981 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253981, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253981 BINDING SITE, designated SEQ ID:45865, to the nucleotide sequence of VGAM643 RNA, herein designated VGAM RNA, also designated SEQ ID:3354.

[26816] Another function of VGAM643 is therefore inhibition of LOC253981 (Accession XM\_171064). Accordingly, utilities of VGAM643 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253981. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 644 (VGAM644) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26817] VGAM644 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM644 was detected is described

hereinabove with reference to Figs. 1–8.

[26818] VGAM644 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Parvovirus H1. VGAM644 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26819] VGAM644 gene encodes a VGAM644 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM644 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM644 precursor RNA is designated SEQ ID:630, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:630 is located at position 129 relative to the genome of Parvovirus H1.

[26820] VGAM644 precursor RNA folds onto itself, forming VGAM644 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed–reversed sequence of the nu–

cleotide sequence of the second half thereof.

[26821] An enzyme complex designated DICER COMPLEX, `dices` the VGAM644 folded precursor RNA into VGAM644 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM644 RNA is designated SEQ ID:3355, and is provided hereinbelow with reference to the sequence listing part.

[26822] VGAM644 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM644 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM644 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26823] VGAM644 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM644 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM644 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM644 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM644 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26824] The complementary binding of VGAM644 RNA, herein designated VGAM RNA, to host target binding sites on VGAM644 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM644 host target RNA into VGAM644 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26825] It is appreciated that VGAM644 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM644 host target genes. The mRNA of each one of this plurality of VGAM644 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM644 RNA, herein designated VGAM RNA, and which when bound by VGAM644 RNA causes inhibition of translation of respective one or more VGAM644 host target proteins.

[26826] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM644 gene, herein designated VGAM GENE, on one or more VGAM644 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated



only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26827] It is yet further appreciated that a function of VGAM644 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of viral infection by Parvovirus H1. Specific functions, and accordingly utilities, of VGAM644 correlate with, and may be deduced from, the identity of the host target genes which VGAM644 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26828] Nucleotide sequences of the VGAM644 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM644 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM644 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM644 are further described hereinbelow with reference to Table 1.

[26829] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM644 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM644 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26830] As mentioned hereinabove with reference to Fig. 1, a function of VGAM644 gene, herein designated VGAM is inhibition of expression of VGAM644 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM644 correlate with, and may be deduced from, the identity of the target genes which VGAM644 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26831] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_004996) is a VGAM644 host target gene. ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABCC1, corresponding to HOST TARGET binding sites such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3, designated SEQ ID:11438, SEQ ID:21282 and SEQ ID:21286 respectively, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26832] A function of VGAM644 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_004996), a gene which may participate directly in the active transport of drugs into sub-cellular organelles or influence drug distribution indirectly. Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCC1. The function of ABCC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM479.WW Domain Containing Oxidoreductase (WWOX, Accession NM\_016373) is another VGAM644 host target gene. WWOX BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WWOX, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WWOX BINDING SITE, designated SEQ ID:18503, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26833] Another function of VGAM644 is therefore inhibition of WW Domain Containing Oxidoreductase (WWOX, Accession NM\_016373), a gene which involves in protein-protein interactions and may contribute to the biologic consequences of DNA instability. Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WWOX. The function of WWOX has been established by previous studies. To identify genes mapping to the chromosome region 16q23.3–q24.1, an area commonly affected by allelic loss in breast cancer, Bednarek et al. (2000) generated a detailed physical map of the genomic region spanning STS markers D16S518 and D16S516. By use of shotgun genomic sequencing as well as isolation and analysis of transcripts mapping to this region, they identified and cloned a novel gene, the genomic structure of which spanned the entire region. They designated the gene

WWOX because it contains 2 WW domains coupled to a region with high homology to the short-chain dehydrogenase/reductase (SRD) family of enzymes. The WWOX gene contains 9 exons and encodes a 414-amino acid protein. Bednarek et al. (2000) performed a mutation screen of WWOX exons in a panel of breast cancer lines, most of which were hemizygous for the 16q genomic region indicated. They found no evidence of mutations, indicating that WWOX is probably not a tumor suppressor gene. However, they observed that 1 case of homozygous deletion and 2 previously described translocation breakpoints map to intronic regions of this gene. They speculated that the WWOX gene may span the region of the common fragile site FRA16D. Northern blot analysis detected overexpression of a 2.2-kb WWOX transcript in breast cancer cell lines when compared to normal tissues. The highest normal expression was detected in hormonally regulated tissues such as testis, ovary, and prostate. This expression pattern and the presence of an SRD domain and specific amino acid features suggested a role for WWOX in steroid metabolism. The presence of WW domains indicated a role in protein-protein interactions. Chang et al. (2001) showed that the homologous mouse protein, Wox1, is an

essential mediator of tumor necrosis factor- $\alpha$ -induced apoptosis. Furthermore, mouse Wox1 protein binds directly to p53 (OMIM Ref. No. 191170), and blocking Wox1 by expression of antisense mRNA abolishes p53-mediated apoptosis in NIH 3T3 cells. The high conservation of WWOX protein between Homo sapiens and Mus musculus (93% identity) supported a similar, important role in apoptosis for human WWOX. In a mutation screen of WWOX in human cancer, Paige et al. (2001) demonstrated homozygous deletion of WWOX exons from ovarian cancer cells and 3 different tumor cell lines. They also identified an internally deleted WWOX transcript from a further primary ovarian tumor. In 3 of these samples the deletions resulted in frameshifts, and in each case the resulting WWOX transcripts lacked part, or all, of the short-chain dehydrogenase domain and the putative mitochondrial localization signal. Sequencing demonstrated several missense polymorphisms in tumor cell lines and identified a high level of single nucleotide polymorphism within the WWOX gene. The authors stated that the evidence strengthened the case for WWOX as a tumor suppressor gene in ovarian cancer and other tumor types. Bednarek et al. (2001) presented data indicating that WWOX behaves

as a potent suppressor of tumor growth and suggesting that abnormalities affecting this gene at the genomic and transcriptional level may be relevant in carcinogenesis. Two of the most frequently observed fragile sites in humans, FRA3B and FRA16D, show a high frequency of breakage and colocalize with genes crossing large regions of breakage. At FRA3B, the fragile histidine triad gene (FHIT; 601153) spans more than 1 Mb, and at FRA16D the WWOX gene spans more than 750 kb. In the mouse, the common fragile site Fra14A2 and the Fhit gene are conserved in the homologous region of the genome. Krummel et al. (2002) positioned the mouse homolog of WWOX (Wox1) at band 8E1 of the mouse genome, colocalizing with Fra8E1. The sequence from this region, including introns, is highly conserved over at least a 100-kb region. This evolutionary conservation suggests that the 2 most active common fragile sites share many features and that they and their associated genes may be necessary for cell survival.

[26834] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26835] Kuroki, T.; Trapasso, F.; Shiraishi, T.; Alder, H.; Mimori, K.;

Mori, M.; Croce, C. M. : Genetic alterations of the tumor suppressor gene WWOX in esophageal squamous cell carcinoma. Cancer Res. 62: 2258–2260, 2002. ; and

[26836] Paige, A. J. W.; Taylor, K. J.; Taylor, C.; Hillier, S. G.; Farrington, S.; Scott, D.; Porteous, D. J.; Smyth, J. F.; Gabra, H.; Watson, J. E. V. : WWOX: a candidate tumor suppressor ge.

[26837] Further studies establishing the function and utilities of WWOX are found in John Hopkins OMIM database record ID 605131, and in cited publications numbered 7084–708 and 4651–2874 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZp762E1511 (Accession XM\_003460) is another VGAM644 host target gene. DKFZp762E1511 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp762E1511, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762E1511 BINDING SITE, designated SEQ ID:29935, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.



[26838] Another function of VGAM644 is therefore inhibition of DKFZp762E1511 (Accession XM\_003460). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp762E1511. KIAA0534 (Accession XM\_049349) is another VGAM644 host target gene. KIAA0534 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0534, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0534 BINDING SITE, designated SEQ ID:35388, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26839] Another function of VGAM644 is therefore inhibition of KIAA0534 (Accession XM\_049349). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0534. KIAA1580 (Accession XM\_045271) is another VGAM644 host target gene. KIAA1580 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1580, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1580 BINDING SITE, designated SEQ ID:34405, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26840] Another function of VGAM644 is therefore inhibition of KIAA1580 (Accession XM\_045271). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1580. Retinoic Acid Induced 17 (RAI17, Accession XM\_166091) is another VGAM644 host target gene. RAI17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAI17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAI17 BINDING SITE, designated SEQ ID:43863, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26841] Another function of VGAM644 is therefore inhibition of Retinoic Acid Induced 17 (RAI17, Accession XM\_166091). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with RAI17. SBBI26 (Accession NM\_018846) is another VGAM644 host target gene. SBBI26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SBBI26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SBBI26 BINDING SITE, designated SEQ ID:20831, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26842] Another function of VGAM644 is therefore inhibition of SBBI26 (Accession NM\_018846). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SBBI26. LOC220018 (Accession XM\_167816) is another VGAM644 host target gene. LOC220018 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220018, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220018 BINDING SITE, designated SEQ ID:44853, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA,

also designated SEQ ID:3355.

[26843] Another function of VGAM644 is therefore inhibition of LOC220018 (Accession XM\_167816). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220018. LOC254251 (Accession XM\_171088) is another VGAM644 host target gene. LOC254251 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254251 BINDING SITE, designated SEQ ID:45897, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26844] Another function of VGAM644 is therefore inhibition of LOC254251 (Accession XM\_171088). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254251. LOC57086 (Accession NM\_020351) is another VGAM644 host target gene. LOC57086 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC57086, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57086 BINDING SITE, designated SEQ ID:21616, to the nucleotide sequence of VGAM644 RNA, herein designated VGAM RNA, also designated SEQ ID:3355.

[26845] Another function of VGAM644 is therefore inhibition of LOC57086 (Accession NM\_020351). Accordingly, utilities of VGAM644 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57086. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 645 (VGAM645) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26846] VGAM645 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM645 was detected is described hereinabove with reference to Figs. 1–8.

[26847] VGAM645 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Parvovirus H1. VGAM645

host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26848] VGAM645 gene encodes a VGAM645 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM645 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM645 precursor RNA is designated SEQ ID:631, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:631 is located at position 1 relative to the genome of Parvovirus H1.

[26849] VGAM645 precursor RNA folds onto itself, forming VGAM645 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26850] An enzyme complex designated DICER COMPLEX, `dices` the VGAM645 folded precursor RNA into VGAM645 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM645 RNA is designated SEQ ID:3356, and is provided hereinbelow with reference to the sequence listing part.

[26851] VGAM645 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM645 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM645 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26852] VGAM645 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM645 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM645 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM645 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM645 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26853] The complementary binding of VGAM645 RNA, herein designated VGAM RNA, to host target binding sites on VGAM645 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM645 host target RNA into VGAM645 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target



protein is therefore outlined by a broken line.

[26854] It is appreciated that VGAM645 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM645 host target genes. The mRNA of each one of this plurality of VGAM645 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM645 RNA, herein designated VGAM RNA, and which when bound by VGAM645 RNA causes inhibition of translation of respective one or more VGAM645 host target proteins.

[26855] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM645 gene, herein designated VGAM GENE, on one or more VGAM645 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26856] It is yet further appreciated that a function of VGAM645 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM645 include diagnosis, prevention and treatment of viral infection by Parvovirus H1. Specific functions, and accordingly utilities, of VGAM645 correlate with, and may be deduced from, the identity of the host target genes which VGAM645 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26857] Nucleotide sequences of the VGAM645 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM645 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM645 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM645 are further described hereinbelow with reference to Table 1.

[26858] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM645 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM645 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26859] As mentioned hereinabove with reference to Fig. 1, a function of VGAM645 gene, herein designated VGAM is inhibition of expression of VGAM645 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM645 correlate with, and may be deduced from, the identity of the target genes which VGAM645 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26860] Zinc Finger Protein 2 (A1-5) (ZNF2, Accession NM\_021088) is a VGAM645 host target gene. ZNF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF2 BINDING SITE, designated SEQ ID:22065, to the nucleotide sequence of VGAM645 RNA, herein designated VGAM

RNA, also designated SEQ ID:3356.

- [26861] A function of VGAM645 is therefore inhibition of Zinc Finger Protein 2 (A1–5) (ZNF2, Accession NM\_021088). Accordingly, utilities of VGAM645 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 646 (VGAM646) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [26862] VGAM646 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM646 was detected is described hereinabove with reference to Figs. 1–8.
- [26863] VGAM646 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lactate Dehydrogenase–elevating Virus. VGAM646 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.
- [26864] VGAM646 gene encodes a VGAM646 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM646 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM646 precursor RNA is designated SEQ ID:632, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:632 is located at position 1908 relative to the genome of Lactate Dehydrogenase-elevating Virus.

[26865] VGAM646 precursor RNA folds onto itself, forming VGAM646 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26866] An enzyme complex designated DICER COMPLEX, `dices` the VGAM646 folded precursor RNA into VGAM646 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM646 RNA is designated SEQ ID:3357, and is provided hereinbelow with reference to the sequence listing part.

[26867] VGAM646 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM646 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM646 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26868] VGAM646 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM646 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM646 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM646 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM646 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26869] The complementary binding of VGAM646 RNA, herein designated VGAM RNA, to host target binding sites on VGAM646 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM646 host target RNA into VGAM646 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26870] It is appreciated that VGAM646 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM646 host target genes. The mRNA of

each one of this plurality of VGAM646 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM646 RNA, herein designated VGAM RNA, and which when bound by VGAM646 RNA causes inhibition of translation of respective one or more VGAM646 host target proteins.

[26871] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM646 gene, herein designated VGAM GENE, on one or more VGAM646 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science



294,779 (2001)).

[26872] It is yet further appreciated that a function of VGAM646 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of viral infection by Lactate Dehydrogenase-elevating Virus. Specific functions, and accordingly utilities, of VGAM646 correlate with, and may be deduced from, the identity of the host target genes which VGAM646 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26873] Nucleotide sequences of the VGAM646 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM646 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM646 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM646 are further described hereinbelow with reference to Table 1.

[26874] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM646 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM646 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[26875] As mentioned hereinabove with reference to Fig. 1, a function of VGAM646 gene, herein designated VGAM is inhibition of expression of VGAM646 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM646 correlate with, and may be deduced from, the identity of the target genes which VGAM646 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26876] ABH (Accession XM\_007409) is a VGAM646 host target gene. ABH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABH BINDING SITE, designated SEQ ID:30054, to the nucleotide sequence of VGAM646 RNA, herein designated VGAM RNA, also designated SEQ ID:3357.

[26877] A function of VGAM646 is therefore inhibition of ABH (Accession XM\_007409). Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABH. Ox-

oxidative-stress Responsive 1 (OSR1, Accession NM\_005109) is another VGAM646 host target gene. OSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSR1 BINDING SITE, designated SEQ ID:11586, to the nucleotide sequence of VGAM646 RNA, herein designated VGAM RNA, also designated SEQ ID:3357.

[26878] Another function of VGAM646 is therefore inhibition of Oxidative-stress Responsive 1 (OSR1, Accession NM\_005109), a gene which mediates stress-activated signals. Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OSR1. The function of OSR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM538.KIAA0408 (Accession NM\_014702) is another VGAM646 host target gene. KIAA0408 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0408, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0408 BINDING SITE, designated SEQ ID:16231, to the nucleotide sequence of VGAM646 RNA, herein designated VGAM RNA, also designated SEQ ID:3357.

[26879] Another function of VGAM646 is therefore inhibition of KIAA0408 (Accession NM\_014702). Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0408. PA26 (Accession NM\_014454) is another VGAM646 host target gene. PA26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PA26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PA26 BINDING SITE, designated SEQ ID:15805, to the nucleotide sequence of VGAM646 RNA, herein designated VGAM RNA, also designated SEQ ID:3357.

[26880] Another function of VGAM646 is therefore inhibition of PA26 (Accession NM\_014454). Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PA26. RENT2 (Accession NM\_015542) is another VGAM646 host target gene. RENT2 BINDING SITE1 and RENT2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RENT2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RENT2 BINDING SITE1 and RENT2 BINDING SITE2, designated SEQ ID:17802 and SEQ ID:27908 respectively, to the nucleotide sequence of VGAM646 RNA, herein designated VGAM RNA, also designated SEQ ID:3357.

[26881] Another function of VGAM646 is therefore inhibition of RENT2 (Accession NM\_015542). Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RENT2. LOC152245 (Accession XM\_098182) is another VGAM646 host target gene. LOC152245 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152245, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152245 BINDING

SITE, designated SEQ ID:41449, to the nucleotide sequence of VGAM646 RNA, herein designated VGAM RNA, also designated SEQ ID:3357.

[26882] Another function of VGAM646 is therefore inhibition of LOC152245 (Accession XM\_098182). Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152245. LOC200933 (Accession XM\_117294) is another VGAM646 host target gene. LOC200933 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200933, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200933 BINDING SITE, designated SEQ ID:43364, to the nucleotide sequence of VGAM646 RNA, herein designated VGAM RNA, also designated SEQ ID:3357.

[26883] Another function of VGAM646 is therefore inhibition of LOC200933 (Accession XM\_117294). Accordingly, utilities of VGAM646 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200933. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 647 (VGAM647) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26884] VGAM647 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM647 was detected is described hereinabove with reference to Figs. 1–8.

[26885] VGAM647 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Acute Bee Paralysis Virus. VGAM647 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26886] VGAM647 gene encodes a VGAM647 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM647 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM647 precursor RNA is designated SEQ ID:633, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:633 is located at position 5839 relative to the genome of Acute

## Bee Paralysis Virus.

[26887] VGAM647 precursor RNA folds onto itself, forming VGAM647 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26888] An enzyme complex designated DICER COMPLEX, `dices` the VGAM647 folded precursor RNA into VGAM647 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 57%) nucleotide sequence of VGAM647 RNA is designated SEQ ID:3358, and is provided hereinbelow with reference to the sequence listing part.

[26889] VGAM647 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger



RNA, VGAM647 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM647 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26890] VGAM647 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM647 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM647 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM647 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM647 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[26891] The complementary binding of VGAM647 RNA, herein designated VGAM RNA, to host target binding sites on VGAM647 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM647 host target RNA into VGAM647 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26892] It is appreciated that VGAM647 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM647 host target genes. The mRNA of each one of this plurality of VGAM647 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM647 RNA, herein designated VGAM RNA, and which when bound by VGAM647 RNA causes inhibition of translation of respective one or more VGAM647 host target proteins.

[26893] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM647 gene, herein designated VGAM GENE, on one or more VGAM647 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26894] It is yet further appreciated that a function of VGAM647 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of viral infection by Acute Bee Paralysis Virus. Specific functions, and accordingly utilities, of VGAM647

correlate with, and may be deduced from, the identity of the host target genes which VGAM647 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26895] Nucleotide sequences of the VGAM647 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM647 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM647 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM647 are further described hereinbelow with reference to Table 1.

[26896] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM647 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM647 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26897] As mentioned hereinabove with reference to Fig. 1, a function of VGAM647 gene, herein designated VGAM is inhibition of expression of VGAM647 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM647 correlate with, and may be deduced

from, the identity of the target genes which VGAM647 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26898] Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 2 (p85 beta) (PIK3R2, Accession NM\_005027) is a VGAM647 host target gene. PIK3R2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIK3R2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIK3R2 BINDING SITE, designated SEQ ID:11466, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26899] A function of VGAM647 is therefore inhibition of Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 2 (p85 beta) (PIK3R2, Accession NM\_005027), a gene which acts as an adapter and is regulatory subunit (p85 beta) of phosphatidylinositol 3-kinase. Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIK3R2. The function of PIK3R2 has been established by previous studies. Otsu et al. (1991) showed that the bovine

PI3-kinase p85 subunit consists of 2 closely related proteins, p85-alpha (OMIM Ref. No. 171833) and p85-beta. They cloned cDNAs encoding both p85 subunits, each of which is 724 amino acids long. The subunits share 62% amino acid identity across their entire length. Both sequences contain an N-terminal SH3 region, 2 SH2 regions, and a region of homology to BCR (OMIM Ref. No. 151410). Functional expression studies showed that both p85 subunits bind to tyrosine kinase receptors. Janssen et al. (1998) analyzed DNA from a patient with chronic myeloproliferative disorder. They identified an oncogenic fusion of the 5-prime end of p85-beta and the 3-prime end of HUMORF8 (OMIM Ref. No. 603158). Janssen et al. (1998) determined the human p85-beta cDNA sequence.

[26900] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26901] Janssen, J. W. G.; Schleithoff, L.; Bartram, C. R.; Schulz, A. S. : An oncogenic fusion product of the phosphatidylinositol 3-kinase p85-beta subunit and HUMORF8, a putative deubiquitinating enzyme. *Oncogene* 16: 1767-1772, 1998. ; and

[26902] Otsu, M.; Hiles, I.; Gout, I.; Fry, M. J.; Ruiz-Larrea, F.;

Panayotou, G.; Thompson, A.; Dhand, R.; Hsuan, J.; Totty, N.; Smith, A. D.; Morgan, S. J.; Courtneidge, S. A.; Parker, P. J.;

[26903] Further studies establishing the function and utilities of PIK3R2 are found in John Hopkins OMIM database record ID 603157, and in cited publications numbered 2427, 383 and 3842 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_002838) is another VGAM647 host target gene. PTPRC BINDING SITE1 and PTPRC BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PTPRC, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTPRC BINDING SITE1 and PTPRC BINDING SITE2, designated SEQ ID:8718 and SEQ ID:28144 respectively, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26904] Another function of VGAM647 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_002838). Accordingly, utilities of VGAM647

include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRC. TAF5 RNA Polymerase II, TATA Box Binding Protein (TBP)–associated Factor, 100kDa (TAF5, Accession NM\_006951) is another VGAM647 host target gene. TAF5 BINDING SITE1 and TAF5 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TAF5, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAF5 BINDING SITE1 and TAF5 BINDING SITE2, designated SEQ ID:13837 and SEQ ID:14337 respectively, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26905] Another function of VGAM647 is therefore inhibition of TAF5 RNA Polymerase II, TATA Box Binding Protein (TBP)–associated Factor, 100kDa (TAF5, Accession NM\_006951), a gene which is involved as a modulator or transducer in various transmembrane signaling systems. Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAF5. The function of TAF5 has been established by previous studies. Dubrovskaya et al. (1996)



characterized a human TAF, called TAFII100 by them, which is homologous to *Drosophila* TAFII80 (65% similar) and yeast TAFII90 (57% similar). They cloned a TAFII100 cDNA that encodes a 799-amino acid polypeptide with a calculated molecular mass of 87.9 kD; however, both endogenous and recombinant proteins have an electrophoretically determined relative mass of 100 kD. By deletional analysis, Dubrovskaya et al. (1996) showed that the C-terminal, WD-40 repeat-containing domain is not required for incorporation into the TFIID complex. Independently, Tanese et al. (1996) cloned and characterized the C-terminal 801 amino acids of TAFII100. They suggested that, since the N-terminal amino acid sequence obtained from sequencing the endogenous protein is different from the N-terminal sequence predicted by the cloned gene, the full-length TAFII100 gene (also symbolized TAF2D) probably encodes a short peptide sequence upstream of their putative initiation methionine and that of Dubrovskaya et al. (1996).

[26906] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26907] Dubrovskaya, V.; Lavigne, A.-C.; Davidson, I.; Acker, J.;

Staub, A.; Tora, L. : Distinct domains of hTAFII100 are required for functional interaction with transcription factor TFIIF-beta (RAP30) and incorporation into the TFIID complex. EMBO J. 15: 3702-3712, 1996. ; and

[26908] Tanese, N.; Saluja, D.; Vassallo, M. F.; Chen, J.-L.; Admon, A. : Molecular cloning and analysis of two subunits of the human TFIID complex: hTAFII130 and hTAFII100. Proc. Nat. Acad. Sc.

[26909] Further studies establishing the function and utilities of TAF5 are found in John Hopkins OMIM database record ID 601787, and in cited publications numbered 1276-1279 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0061 (Accession XM\_043094) is another VGAM647 host target gene. KIAA0061 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0061, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0061 BINDING SITE, designated SEQ ID:33894, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26910] Another function of VGAM647 is therefore inhibition of KIAA0061 (Accession XM\_043094). Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0061. NAG73 (Accession NM\_032570) is another VGAM647 host target gene. NAG73 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NAG73, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAG73 BINDING SITE, designated SEQ ID:26301, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26911] Another function of VGAM647 is therefore inhibition of NAG73 (Accession NM\_032570). Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAG73. P450RAI-2 (Accession NM\_019885) is another VGAM647 host target gene. P450RAI-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P450RAI-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P450RAI-2 BINDING SITE, designated SEQ ID:21266, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26912] Another function of VGAM647 is therefore inhibition of P450RAI-2 (Accession NM\_019885). Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P450RAI-2. LOC123242 (Accession XM\_063548) is another VGAM647 host target gene. LOC123242 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC123242, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC123242 BINDING SITE, designated SEQ ID:37249, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26913] Another function of VGAM647 is therefore inhibition of LOC123242 (Accession XM\_063548). Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC123242. LOC253001 (Accession XM\_171711) is another VGAM647 host target gene. LOC253001 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253001, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253001 BINDING SITE, designated SEQ ID:46063, to the nucleotide sequence of VGAM647 RNA, herein designated VGAM RNA, also designated SEQ ID:3358.

[26914] Another function of VGAM647 is therefore inhibition of LOC253001 (Accession XM\_171711). Accordingly, utilities of VGAM647 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253001. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 648 (VGAM648) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26915] VGAM648 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM648 was detected is described hereinabove with reference to Figs. 1–8.

[26916] VGAM648 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Acute Bee Paralysis Virus. VGAM648 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26917] VGAM648 gene encodes a VGAM648 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM648 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM648 precursor RNA is designated SEQ ID:634, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:634 is located at position 5074 relative to the genome of Acute Bee Paralysis Virus.

[26918] VGAM648 precursor RNA folds onto itself, forming VGAM648 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26919] An enzyme complex designated DICER COMPLEX, `dices` the VGAM648 folded precursor RNA into VGAM648 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 86%) nucleotide sequence of VGAM648 RNA is designated SEQ ID:3359, and is provided hereinbelow with reference to the sequence listing part.

[26920] VGAM648 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM648 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM648 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26921] VGAM648 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM648 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM648 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM648 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM648 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[26922] The complementary binding of VGAM648 RNA, herein designated VGAM RNA, to host target binding sites on



VGAM648 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM648 host target RNA into VGAM648 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26923] It is appreciated that VGAM648 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM648 host target genes. The mRNA of each one of this plurality of VGAM648 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM648 RNA, herein designated VGAM RNA, and which when bound by VGAM648 RNA causes inhibition of translation of respective one or more VGAM648 host target proteins.

[26924] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM648 gene, herein designated VGAM GENE, on one or more VGAM648 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26925] It is yet further appreciated that a function of VGAM648 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of viral infection by Acute Bee Paralysis Virus. Specific functions, and accordingly utilities, of VGAM648 correlate with, and may be deduced from, the identity of the host target genes which VGAM648 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26926] Nucleotide sequences of the VGAM648 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM648 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM648 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM648 are further described hereinbelow with reference to Table 1.

[26927] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM648 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM648 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26928] As mentioned hereinabove with reference to Fig. 1, a function of VGAM648 gene, herein designated VGAM is inhibition of expression of VGAM648 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM648 correlate with, and may be deduced from, the identity of the target genes which VGAM648 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26929] Cytochrome P450, Subfamily XIX (aromatization of androgens) (CYP19, Accession NM\_000103) is a VGAM648 host target gene. CYP19 BINDING SITE1 and CYP19 BINDING SITE2 are HOST TARGET binding sites found in untrans-

lated regions of mRNA encoded by CYP19, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP19 BINDING SITE1 and CYP19 BINDING SITE2, designated SEQ ID:5561 and SEQ ID:25271 respectively, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26930] A function of VGAM648 is therefore inhibition of Cytochrome P450, Subfamily XIX (aromatization of androgens) (CYP19, Accession NM\_000103), a gene which catalyzes the last steps of estrogen biosynthesis. Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP19. The function of CYP19 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM508. Jerky Homolog (mouse) (JRK, Accession XM\_098818) is another VGAM648 host target gene. JRK BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by JRK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JRK BINDING SITE, designated SEQ ID:41835, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26931] Another function of VGAM648 is therefore inhibition of Jerky Homolog (mouse) (JRK, Accession XM\_098818), a gene which might function as a DNA-binding protein. Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JRK. The function of JRK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM210. Killer Cell Lectin-like Receptor Subfamily G, Member 1 (KLRG1, Accession NM\_005810) is another VGAM648 host target gene. KLRG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KLRG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KLRG1 BINDING SITE, designated SEQ ID:12392, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA,

also designated SEQ ID:3359.

[26932] Another function of VGAM648 is therefore inhibition of Killer Cell Lectin-like Receptor Subfamily G, Member 1 (KLRG1, Accession NM\_005810), a gene which plays a role in host defense;. Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KLRG1. The function of KLRG1 has been established by previous studies. Inhibitory lectin-like receptors expressed on the surface of hematopoietic cells regulate immunocyte effector functions through interactions with specific ligands. For example, major histocompatibility complex (MHC) class I molecules are recognized by natural killer (NK) cells. All of these inhibitory receptors contain a cytoplasmic immunoreceptor tyrosine-based inhibitory motif, or ITIM. Upon MHC I engagement and tyrosine phosphorylation of the ITIM, intracellular tyrosine protein phosphatases such as SHP1 (PTPN6; 176883) are recruited to the ITIM, and an inhibitory signal cascade leads to the abrogation of NK cell activation. By searching an EST database for sequences similar to the ITIM-bearing rat mast cell function-associated antigen (MAFA), Butcher et al. (1998) and Hanke et al. (1998) identified clones encoding KLRG1,

which Butcher et al. (1998) designated 'MAFA-like' (MAFAL). Using PCR analysis on a basophil-like leukemia cell line and human lung mast cells, Lamers et al. (1998) also isolated a cDNA encoding KLRG1, which they called MAFA. The deduced 189-amino acid KLRG1 is a type II transmembrane protein containing a C-type lectin carbohydrate recognition domain, an intracellular ITIM-like motif, and 4 potential N-glycosylation sites. Northern blot analysis by Butcher et al. (1998) detected a 1-kb KLRG1 transcript in spleen, lymph node, and peripheral blood leukocytes. By RT-PCR analysis, Butcher et al. (1998) found expression of KLRG1 in peripheral blood NK cells, a monocytic cell line, and a basophilic leukemia cell line; expression was not found in decidual NK cells, B cells, and T cells.

[26933] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26934] Lamers, M. B. A. C.; Lamont, A. G.; Williams, D. H. : Human MAFA has alternatively spliced variants. *Biochim. Biophys. Acta* 1399: 209-212, 1998. ; and

[26935] Voehringer, D.; Kaufmann, M.; Pircher, H. : Genomic structure, alternative splicing, and physical mapping of

the killer cell lectin-like receptor G1 gene (KLRG1), the mouse homologue of.

[26936] Further studies establishing the function and utilities of KLRG1 are found in John Hopkins OMIM database record ID 604874, and in cited publications numbered 6754–6757 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ERp44 (Accession XM\_088476) is another VGAM648 host target gene. ERp44 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ERp44, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ERp44 BINDING SITE, designated SEQ ID:39725, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26937] Another function of VGAM648 is therefore inhibition of ERp44 (Accession XM\_088476). Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ERp44. FLJ10546 (Accession XM\_002989) is another VGAM648 host target gene. FLJ10546 BINDING SITE is HOST TARGET



binding site found in the 3' untranslated region of mRNA encoded by FLJ10546, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10546 BINDING SITE, designated SEQ ID:29914, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26938] Another function of VGAM648 is therefore inhibition of FLJ10546 (Accession XM\_002989). Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10546. FLJ21438 (Accession XM\_029084) is another VGAM648 host target gene. FLJ21438 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21438, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21438 BINDING SITE, designated SEQ ID:30847, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26939] Another function of VGAM648 is therefore inhibition of

FLJ21438 (Accession XM\_029084). Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21438. KIAA1115 (Accession NM\_014931) is another VGAM648 host target gene. KIAA1115 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1115, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1115 BINDING SITE, designated SEQ ID:17228, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26940] Another function of VGAM648 is therefore inhibition of KIAA1115 (Accession NM\_014931). Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1115. SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily F, Member 1 (SMARCF1, Accession NM\_018450) is another VGAM648 host target gene. SMARCF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SMARCF1, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMARCF1 BINDING SITE, designated SEQ ID:20522, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26941] Another function of VGAM648 is therefore inhibition of SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily F, Member 1 (SMARCF1, Accession NM\_018450). Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMARCF1. LOC90297 (Accession XM\_030742) is another VGAM648 host target gene. LOC90297 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90297, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90297 BINDING SITE, designated SEQ ID:31131, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26942] Another function of VGAM648 is therefore inhibition of

LOC90297 (Accession XM\_030742). Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90297. LOC90785 (Accession XM\_034110) is another VGAM648 host target gene. LOC90785 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90785, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90785 BINDING SITE, designated SEQ ID:32007, to the nucleotide sequence of VGAM648 RNA, herein designated VGAM RNA, also designated SEQ ID:3359.

[26943] Another function of VGAM648 is therefore inhibition of LOC90785 (Accession XM\_034110). Accordingly, utilities of VGAM648 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90785. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 649 (VGAM649) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[26944] VGAM649 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM649 was detected is described hereinabove with reference to Figs. 1–8.

[26945] VGAM649 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Acute Bee Paralysis Virus. VGAM649 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26946] VGAM649 gene encodes a VGAM649 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM649 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM649 precursor RNA is designated SEQ ID:635, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:635 is located at position 5290 relative to the genome of Acute Bee Paralysis Virus.

[26947] VGAM649 precursor RNA folds onto itself, forming VGAM649 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[26948] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM649 folded precursor RNA into VGAM649 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 81%) nucleotide se-  
quence of VGAM649 RNA is designated SEQ ID:3360, and  
is provided hereinbelow with reference to the sequence  
listing part.

[26949] VGAM649 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM649 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM649 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[26950] VGAM649 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM649 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM649 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM649 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM649 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[26951] The complementary binding of VGAM649 RNA, herein designated VGAM RNA, to host target binding sites on VGAM649 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM649 host target RNA into VGAM649 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26952] It is appreciated that VGAM649 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM649 host target genes. The mRNA of each one of this plurality of VGAM649 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM649 RNA, herein designated VGAM RNA, and which when bound by VGAM649 RNA causes inhibition of translation of respective one or more VGAM649 host target proteins.

[26953] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM649 gene, herein designated VGAM GENE, on one or



more VGAM649 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26954] It is yet further appreciated that a function of VGAM649 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of viral infection by Acute Bee Paralysis Virus. Specific functions, and accordingly utilities, of VGAM649 correlate with, and may be deduced from, the identity of the host target genes which VGAM649 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [26955] Nucleotide sequences of the VGAM649 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM649 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM649 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM649 are further described hereinbelow with reference to Table 1.
- [26956] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM649 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM649 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [26957] As mentioned hereinabove with reference to Fig. 1, a function of VGAM649 gene, herein designated VGAM is inhibition of expression of VGAM649 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM649 correlate with, and may be deduced from, the identity of the target genes which VGAM649 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [26958] Forkhead Box E3 (FOX E3, Accession NM\_012186) is a

VGAM649 host target gene. FOXE3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FOXE3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOXE3 BINDING SITE, designated SEQ ID:14470, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26959] A function of VGAM649 is therefore inhibition of Forkhead Box E3 (FOXE3, Accession NM\_012186), a gene which regulates embryonic development. Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOXE3. The function of FOXE3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM632. Low Density Lipoprotein Receptor-related Protein 8, Apolipoprotein E Receptor (LRP8, Accession NM\_004631) is another VGAM649 host target gene. LRP8 BINDING SITE1 and LRP8 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LRP8, corresponding to HOST TARGET binding

sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRP8 BINDING SITE1 and LRP8 BINDING SITE2, designated SEQ ID:11008 and SEQ ID:27132 respectively, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26960] Another function of VGAM649 is therefore inhibition of Low Density Lipoprotein Receptor-related Protein 8, Apolipoprotein E Receptor (LRP8, Accession NM\_004631), a gene which binds vldl and transports it into cells by endocytosis. Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRP8. The function of LRP8 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM191. Trichorhinophalangeal Syndrome I (TRPS1, Accession NM\_014112) is another VGAM649 host target gene. TRPS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of TRPS1 BINDING SITE, designated SEQ ID:15359, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26961] Another function of VGAM649 is therefore inhibition of Trichorhinophalangeal Syndrome I (TRPS1, Accession NM\_014112), a gene which may function as a transcriptional activator protein. Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPS1. The function of TRPS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM172. Wilms Tumor 1 (WT1, Accession NM\_024424) is another VGAM649 host target gene. WT1 BINDING SITE1 through WT1 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by WT1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WT1 BINDING SITE1 through WT1 BINDING SITE4, designated SEQ ID:23669, SEQ ID:23673, SEQ

ID:23677 and SEQ ID:5953 respectively, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26962] Another function of VGAM649 is therefore inhibition of Wilms Tumor 1 (WT1, Accession NM\_024424). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WT1. DAMS (Accession NM\_022001) is another VGAM649 host target gene. DAMS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DAMS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAMS BINDING SITE, designated SEQ ID:22543, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26963] Another function of VGAM649 is therefore inhibition of DAMS (Accession NM\_022001). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAMS. DRIL2 (Accession NM\_006465) is another VGAM649 host target gene. DRIL2 BINDING SITE is HOST TARGET binding

site found in the 3' untranslated region of mRNA encoded by DRIL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRIL2 BINDING SITE, designated SEQ ID:13191, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26964] Another function of VGAM649 is therefore inhibition of DRIL2 (Accession NM\_006465). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRIL2. FLJ13102 (Accession NM\_024887) is another VGAM649 host target gene. FLJ13102 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13102, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13102 BINDING SITE, designated SEQ ID:24346, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26965] Another function of VGAM649 is therefore inhibition of

FLJ13102 (Accession NM\_024887). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13102. FLJ20033 (Accession NM\_017629) is another VGAM649 host target gene. FLJ20033 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20033, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20033 BINDING SITE, designated SEQ ID:19127, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26966] Another function of VGAM649 is therefore inhibition of FLJ20033 (Accession NM\_017629). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20033. FLJ23441 (Accession NM\_024678) is another VGAM649 host target gene. FLJ23441 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ23441, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of FLJ23441 BINDING SITE, designated SEQ ID:23987, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26967] Another function of VGAM649 is therefore inhibition of FLJ23441 (Accession NM\_024678). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23441. KIAA1735 (Accession XM\_113686) is another VGAM649 host target gene. KIAA1735 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1735, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1735 BINDING SITE, designated SEQ ID:42344, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26968] Another function of VGAM649 is therefore inhibition of KIAA1735 (Accession XM\_113686). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1735. MGC2452 (Accession NM\_032644) is another

VGAM649 host target gene. MGC2452 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2452 BINDING SITE, designated SEQ ID:26368, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26969] Another function of VGAM649 is therefore inhibition of MGC2452 (Accession NM\_032644). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2452. LOC150225 (Accession XM\_097870) is another VGAM649 host target gene. LOC150225 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150225, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150225 BINDING SITE, designated SEQ ID:41186, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26970] Another function of VGAM649 is therefore inhibition of LOC150225 (Accession XM\_097870). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150225. LOC157627 (Accession XM\_088347) is another VGAM649 host target gene. LOC157627 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157627, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157627 BINDING SITE, designated SEQ ID:39622, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26971] Another function of VGAM649 is therefore inhibition of LOC157627 (Accession XM\_088347). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157627. LOC196264 (Accession XM\_113683) is another VGAM649 host target gene. LOC196264 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196264, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196264 BINDING SITE, designated SEQ ID:42330, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26972] Another function of VGAM649 is therefore inhibition of LOC196264 (Accession XM\_113683). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196264. LOC253832 (Accession XM\_170739) is another VGAM649 host target gene. LOC253832 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253832, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253832 BINDING SITE, designated SEQ ID:45499, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26973] Another function of VGAM649 is therefore inhibition of LOC253832 (Accession XM\_170739). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC253832. LOC255082 (Accession XM\_172843) is another VGAM649 host target gene. LOC255082 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255082, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255082 BINDING SITE, designated SEQ ID:46116, to the nucleotide sequence of VGAM649 RNA, herein designated VGAM RNA, also designated SEQ ID:3360.

[26974] Another function of VGAM649 is therefore inhibition of LOC255082 (Accession XM\_172843). Accordingly, utilities of VGAM649 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255082. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 650 (VGAM650) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26975] VGAM650 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM650 was detected is described hereinabove with reference to Figs. 1–8.

[26976] VGAM650 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saimiriine Herpesvirus 2. VGAM650 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26977] VGAM650 gene encodes a VGAM650 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM650 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM650 precursor RNA is designated SEQ ID:636, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:636 is located at position 10659 relative to the genome of Saimiriine Herpesvirus 2.

[26978] VGAM650 precursor RNA folds onto itself, forming VGAM650 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[26979] An enzyme complex designated DICER COMPLEX, `dices` the VGAM650 folded precursor RNA into VGAM650 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM650 RNA is designated SEQ ID:3361, and is provided hereinbelow with reference to the sequence listing part.

[26980] VGAM650 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM650 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM650 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[26981] VGAM650 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM650 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM650 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM650 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM650 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[26982] The complementary binding of VGAM650 RNA, herein designated VGAM RNA, to host target binding sites on



VGAM650 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM650 host target RNA into VGAM650 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[26983] It is appreciated that VGAM650 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM650 host target genes. The mRNA of each one of this plurality of VGAM650 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM650 RNA, herein designated VGAM RNA, and which when bound by VGAM650 RNA causes inhibition of translation of respective one or more VGAM650 host target proteins.

[26984] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM650 gene, herein designated VGAM GENE, on one or more VGAM650 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[26985] It is yet further appreciated that a function of VGAM650 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM650 include diagnosis, prevention and treatment of viral infection by Saimiriine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM650 correlate with, and may be deduced from, the identity of the host target genes which VGAM650 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[26986] Nucleotide sequences of the VGAM650 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM650 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM650 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM650 are further described hereinbelow with reference to Table 1.

[26987] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM650 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM650 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[26988] As mentioned hereinabove with reference to Fig. 1, a function of VGAM650 gene, herein designated VGAM is inhibition of expression of VGAM650 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM650 correlate with, and may be deduced from, the identity of the target genes which VGAM650 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[26989] Chorea Acanthocytosis (CHAC, Accession NM\_033305) is a VGAM650 host target gene. CHAC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHAC, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHAC BINDING SITE, designated SEQ ID:27138, to the nucleotide sequence of VGAM650 RNA, herein designated VGAM RNA, also designated SEQ ID:3361.

[26990] A function of VGAM650 is therefore inhibition of Chorea Acanthocytosis (CHAC, Accession NM\_033305), a gene which may regulate the cycling of proteins. Accordingly, utilities of VGAM650 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHAC. The function of CHAC has been established by previous studies. Rampoldi et al. (2001) identified a novel gene in the choreoacanthocytosis (CHAC; 200150) critical region of 9q with an open reading frame of 9,525 nucleotides encoding a 3,174-amino acid protein. Alignment of the RNA with the genomic sequence demonstrated that the gene is organized into 73 exons in a genomic region of about 250 kb. Northern blot analysis detected 2 bands of high molecular weight corresponding to 2 splice variants in all tissues analyzed. Additionally, RT-PCR detected expression in the erythrocyte precursor cell line K562. Rampoldi et al. (2001) found 16 different mutations in in-

dividuals with choreoacanthocytosis. They showed that the CHAC gene encodes an evolutionarily conserved protein and suggested that this protein is involved in protein sorting. In a patient with choreoacanthocytosis (OMIM Ref. No. 200150), Rampoldi et al. (2001) found compound heterozygosity for a 269T→A transversion in exon 4 of the CHAC gene and an insertion of a T between nucleotides 6404 and 6405 in exon 48. The mutations resulted in an ile90→lys (I90K) amino acid change and a frameshift, respectively.

[26991] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[26992] Rampoldi, L.; Dobson-Stone, C.; Rubio, J. P.; Danek, A.; Chalmers, R. M.; Wood, N. W.; Verellen, C.; Ferrer, X.; Mallandrini, A.; Fabrizi, G. M.; Brown, R.; Vance, J.; Pericak-Vance, M.; Rudolf, G.; Carre, S.; Alonso, E.; Manfredi, M.; Nemeth, A. H.; Monaco, A. P. : A conserved sorting-associated protein is mutant in chorea-acanthocytosis. *Nature Genet.* 28: 119–120, 2001. ; and

[26993] Ueno, S.; Maruki, Y.; Nakamura, M.; Tomemori, Y.; Kamae, K.; Tanabe, H.; Yamashita, Y.; Matsuda, S.; Kaneko, S.; Sano, A. : The gene encoding a newly discovered protein,

chorein, is mu.

[26994] Further studies establishing the function and utilities of CHAC are found in John Hopkins OMIM database record ID 605978, and in cited publications numbered 10457 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. HTEX4 (Accession XM\_166378) is another VGAM650 host target gene. HTEX4 BINDING SITE1 through HTEX4 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HTEX4, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HTEX4 BINDING SITE1 through HTEX4 BINDING SITE3, designated SEQ ID:44212, SEQ ID:46648 and SEQ ID:46717 respectively, to the nucleotide sequence of VGAM650 RNA, herein designated VGAM RNA, also designated SEQ ID:3361.

[26995] Another function of VGAM650 is therefore inhibition of HTEX4 (Accession XM\_166378). Accordingly, utilities of VGAM650 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTEX4. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present inven-

tion, referred to here as Viral Genomic Address Messenger 651 (VGAM651) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[26996] VGAM651 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM651 was detected is described hereinabove with reference to Figs. 1–8.

[26997] VGAM651 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM651 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[26998] VGAM651 gene encodes a VGAM651 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM651 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM651 precursor RNA is designated SEQ ID:637, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:637 is located at position 57033 relative to the genome of Meleagrid Herpesvirus 1.

[26999] VGAM651 precursor RNA folds onto itself, forming VGAM651 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27000] An enzyme complex designated DICER COMPLEX, `dices` the VGAM651 folded precursor RNA into VGAM651 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM651 RNA is designated SEQ ID:3362, and is provided hereinbelow with reference to the sequence listing part.

[27001] VGAM651 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM651 host target RNA, herein designated VGAM



HOST TARGET RNA. VGAM651 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27002] VGAM651 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM651 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM651 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM651 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM651 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27003] The complementary binding of VGAM651 RNA, herein designated VGAM RNA, to host target binding sites on VGAM651 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM651 host target RNA into VGAM651 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27004] It is appreciated that VGAM651 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM651 host target genes. The mRNA of each one of this plurality of VGAM651 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM651 RNA, herein designated VGAM RNA, and which when bound by VGAM651 RNA causes inhibition of translation of respective one or more VGAM651 host target proteins.

[27005] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM651 gene, herein designated VGAM GENE, on one or more VGAM651 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27006] It is yet further appreciated that a function of VGAM651 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM651 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM651 correlate with, and may be deduced from, the identity of

the host target genes which VGAM651 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27007] Nucleotide sequences of the VGAM651 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM651 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM651 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM651 are further described hereinbelow with reference to Table 1.

[27008] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM651 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM651 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27009] As mentioned hereinabove with reference to Fig. 1, a function of VGAM651 gene, herein designated VGAM is inhibition of expression of VGAM651 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM651 correlate with, and may be deduced from, the identity of the target genes which VGAM651

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27010] DKFZP434I092 (Accession XM\_042042) is a VGAM651 host target gene. DKFZP434I092 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP434I092, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434I092 BINDING SITE, designated SEQ ID:33674, to the nucleotide sequence of VGAM651 RNA, herein designated VGAM RNA, also designated SEQ ID:3362.

[27011] A function of VGAM651 is therefore inhibition of DKFZP434I092 (Accession XM\_042042). Accordingly, utilities of VGAM651 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434I092. KIAA0556 (Accession XM\_044632) is another VGAM651 host target gene. KIAA0556 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA0556 BINDING SITE, designated SEQ ID:34252, to the nucleotide sequence of VGAM651 RNA, herein designated VGAM RNA, also designated SEQ ID:3362.

[27012] Another function of VGAM651 is therefore inhibition of KIAA0556 (Accession XM\_044632). Accordingly, utilities of VGAM651 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0556. LIG-1 (Accession XM\_033712) is another VGAM651 host target gene. LIG-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LIG-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LIG-1 BINDING SITE, designated SEQ ID:31951, to the nucleotide sequence of VGAM651 RNA, herein designated VGAM RNA, also designated SEQ ID:3362.

[27013] Another function of VGAM651 is therefore inhibition of LIG-1 (Accession XM\_033712). Accordingly, utilities of VGAM651 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LIG-1. LOC164382 (Accession XM\_104390) is another VGAM651 host target gene. LOC164382 BINDING SITE is HOST TAR-

GET binding site found in the 3' untranslated region of mRNA encoded by LOC164382, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164382 BINDING SITE, designated SEQ ID:42163, to the nucleotide sequence of VGAM651 RNA, herein designated VGAM RNA, also designated SEQ ID:3362.

[27014] Another function of VGAM651 is therefore inhibition of LOC164382 (Accession XM\_104390). Accordingly, utilities of VGAM651 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC164382. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 652 (VGAM652) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27015] VGAM652 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM652 was detected is described hereinabove with reference to Figs. 1-8.

[27016] VGAM652 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM652 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27017] VGAM652 gene encodes a VGAM652 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM652 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM652 precursor RNA is designated SEQ ID:638, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:638 is located at position 62005 relative to the genome of Meleagrid Herpesvirus 1.

[27018] VGAM652 precursor RNA folds onto itself, forming VGAM652 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-



cleotide sequence of the second half thereof.

[27019] An enzyme complex designated DICER COMPLEX, `dices` the VGAM652 folded precursor RNA into VGAM652 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 54%) nucleotide sequence of VGAM652 RNA is designated SEQ ID:3363, and is provided hereinbelow with reference to the sequence listing part.

[27020] VGAM652 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM652 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM652 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27021] VGAM652 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM652 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM652 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM652 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM652 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[27022] The complementary binding of VGAM652 RNA, herein designated VGAM RNA, to host target binding sites on VGAM652 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM652 host target RNA into VGAM652 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27023] It is appreciated that VGAM652 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM652 host target genes. The mRNA of each one of this plurality of VGAM652 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM652 RNA, herein designated VGAM RNA, and which when bound by VGAM652 RNA causes inhibition of translation of respective one or more VGAM652 host target proteins.

[27024] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM652 gene, herein designated VGAM GENE, on one or more VGAM652 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27025] It is yet further appreciated that a function of VGAM652 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM652 correlate with, and may be deduced from, the identity of the host target genes which VGAM652 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27026] Nucleotide sequences of the VGAM652 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM652 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM652 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM652 are further described hereinbelow with reference to Table 1.

[27027] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM652 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM652 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27028] As mentioned hereinabove with reference to Fig. 1, a function of VGAM652 gene, herein designated VGAM is inhibition of expression of VGAM652 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM652 correlate with, and may be deduced from, the identity of the target genes which VGAM652 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27029] A Disintegrin and Metalloproteinase Domain 29 (ADAM29, Accession XM\_113428) is a VGAM652 host target gene. ADAM29 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ADAM29, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of ADAM29 BINDING SITE, designated SEQ ID:42261, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27030] A function of VGAM652 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 29 (ADAM29, Accession XM\_113428), a gene which Testis-specific member of ADAM family of zinc metalloproteases. Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM29. The function of ADAM29 has been established by previous studies. ADAMs are a family of cell surface proteins with a domain structure composed of a signal sequence, a prodomain with a cysteine switch, a metalloproteinase-like domain, a disintegrin-like domain, a cysteine-rich domain, a transmembrane domain, and a C-terminal cytoplasmic domain. Members of this family have been implicated in a variety of biologic processes involving cell-cell and cell-matrix interactions, including fertilization, muscle development, and neurogenesis. By searching a DNA sequence database, Cerretti et al. (1999) identified 2 ESTs representing the novel ADAMs ADAM29

and ADAM30 (OMIM Ref. No. 604779). The ADAM29 EST encodes a polypeptide with sequence similarity to the cysteine-rich region of ADAM20 (OMIM Ref. No. 603712). Cerretti et al. (1999) screened a human testis cDNA library with the ADAM29 EST and isolated cDNAs encoding 3 forms of ADAM29 that differ in the cytoplasmic domain. By searching an EST database using ADAM20 as the query, Xu et al. (1999) identified an ADAM29 EST. Using a PCR-based 'walking' strategy, they cloned a full-length ADAM29 coding sequence. By radiation hybrid mapping, Xu et al. (1999) mapped the ADAM29 gene to 4q34.2-qter. Cerretti et al. (1999) mapped the ADAM29 gene to 4q34 using radiation hybrid mapping.

[27031] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27032] Cerretti, D. P.; DuBose, R. F.; Black, R. A.; Nelson, N. : Isolation of two novel metalloproteinase-disintegrin (ADAM) cDNAs that show testis-specific gene expression. Biochem. Biophys. Res. Commun. 263: 810-815, 1999. ; and

[27033] Xu, R.; Cai, J.; Xu, T.; Zhou, W.; Ying, B.; Deng, K.; Zhao, S.; Li, C. : Molecular cloning and mapping of a novel ADAM

gene (ADAM29) to human chromosome 4. Genomics 62: 537–539, 1999.

[27034] Further studies establishing the function and utilities of ADAM29 are found in John Hopkins OMIM database record ID 604778, and in cited publications numbered 6649–6650 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neural Precursor Cell Expressed, Developmentally Down-regulated 4 (NEDD4, Accession XM\_046129) is another VGAM652 host target gene. NEDD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEDD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEDD4 BINDING SITE, designated SEQ ID:34691, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27035] Another function of VGAM652 is therefore inhibition of Neural Precursor Cell Expressed, Developmentally Down-regulated 4 (NEDD4, Accession XM\_046129), a gene which ubiquitinates regulatory proteins involved in transcription. Accordingly, utilities of VGAM652 include diagnosis, pre-



vention and treatment of diseases and clinical conditions associated with NEDD4. The function of NEDD4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM209. E2F Transcription Factor 6 (E2F6, Accession NM\_001952) is another VGAM652 host target gene. E2F6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by E2F6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of E2F6 BINDING SITE, designated SEQ ID:7675, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27036] Another function of VGAM652 is therefore inhibition of E2F Transcription Factor 6 (E2F6, Accession NM\_001952). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with E2F6. ENDOGLYX1 (Accession NM\_024756) is another VGAM652 host target gene. ENDOGLYX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

ENDOGLYX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ENDOGLYX1 BINDING SITE, designated SEQ ID:24102, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27037] Another function of VGAM652 is therefore inhibition of ENDOGLYX1 (Accession NM\_024756). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ENDOGLYX1. FLJ22795 (Accession NM\_025084) is another VGAM652 host target gene. FLJ22795 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22795, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22795 BINDING SITE, designated SEQ ID:24687, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27038] Another function of VGAM652 is therefore inhibition of FLJ22795 (Accession NM\_025084). Accordingly, utilities of

VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22795. MGC22014 (Accession XM\_035307) is another VGAM652 host target gene. MGC22014 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC22014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC22014 BINDING SITE, designated SEQ ID:32215, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27039] Another function of VGAM652 is therefore inhibition of MGC22014 (Accession XM\_035307). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC22014. LOC145717 (Accession XM\_039771) is another VGAM652 host target gene. LOC145717 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145717, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC145717 BINDING SITE, designated SEQ ID:33188, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27040] Another function of VGAM652 is therefore inhibition of LOC145717 (Accession XM\_039771). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145717. LOC145725 (Accession XM\_085211) is another VGAM652 host target gene. LOC145725 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145725, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145725 BINDING SITE, designated SEQ ID:37945, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27041] Another function of VGAM652 is therefore inhibition of LOC145725 (Accession XM\_085211). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145725. LOC145732 (Accession XM\_085218) is another VGAM652 host target gene. LOC145732 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145732, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145732 BINDING SITE, designated SEQ ID:37954, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27042] Another function of VGAM652 is therefore inhibition of LOC145732 (Accession XM\_085218). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145732. LOC149076 (Accession XM\_086415) is another VGAM652 host target gene. LOC149076 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC149076, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149076 BINDING SITE, designated SEQ ID:38636, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27043] Another function of VGAM652 is therefore inhibition of

LOC149076 (Accession XM\_086415). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149076. LOC196326 (Accession XM\_118268) is another VGAM652 host target gene. LOC196326 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196326, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196326 BINDING SITE, designated SEQ ID:43576, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27044] Another function of VGAM652 is therefore inhibition of LOC196326 (Accession XM\_118268). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196326. LOC196957 (Accession XM\_113789) is another VGAM652 host target gene. LOC196957 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196957, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC196957 BINDING SITE, designated SEQ ID:42427, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27045] Another function of VGAM652 is therefore inhibition of LOC196957 (Accession XM\_113789). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196957. LOC196961 (Accession XM\_113790) is another VGAM652 host target gene. LOC196961 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196961, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196961 BINDING SITE, designated SEQ ID:42436, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27046] Another function of VGAM652 is therefore inhibition of LOC196961 (Accession XM\_113790). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196961. LOC197138 (Accession XM\_113829) is an-

other VGAM652 host target gene. LOC197138 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC197138, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197138 BINDING SITE, designated SEQ ID:42454, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27047] Another function of VGAM652 is therefore inhibition of LOC197138 (Accession XM\_113829). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197138. LOC220537 (Accession XM\_165406) is another VGAM652 host target gene. LOC220537 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC220537, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220537 BINDING SITE, designated SEQ ID:43620, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.



[27048] Another function of VGAM652 is therefore inhibition of LOC220537 (Accession XM\_165406). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220537. LOC245727 (Accession XM\_165913) is another VGAM652 host target gene. LOC245727 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC245727, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC245727 BINDING SITE, designated SEQ ID:43795, to the nucleotide sequence of VGAM652 RNA, herein designated VGAM RNA, also designated SEQ ID:3363.

[27049] Another function of VGAM652 is therefore inhibition of LOC245727 (Accession XM\_165913). Accordingly, utilities of VGAM652 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC245727. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 653 (VGAM653) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[27050] VGAM653 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM653 was detected is described hereinabove with reference to Figs. 1–8.

[27051] VGAM653 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM653 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27052] VGAM653 gene encodes a VGAM653 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM653 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM653 precursor RNA is designated SEQ ID:639, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:639 is located at position 62995 relative to the genome of Meleagrid Herpesvirus 1.

[27053] VGAM653 precursor RNA folds onto itself, forming VGAM653 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[27054] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM653 folded precursor RNA into VGAM653 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 80%) nucleotide se-  
quence of VGAM653 RNA is designated SEQ ID:3364, and  
is provided hereinbelow with reference to the sequence  
listing part.

[27055] VGAM653 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM653 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM653 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27056] VGAM653 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM653 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM653 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM653 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM653 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27057] The complementary binding of VGAM653 RNA, herein designated VGAM RNA, to host target binding sites on VGAM653 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM653 host target RNA into VGAM653 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27058] It is appreciated that VGAM653 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM653 host target genes. The mRNA of each one of this plurality of VGAM653 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM653 RNA, herein designated VGAM RNA, and which when bound by VGAM653 RNA causes inhibition of translation of respective one or more VGAM653 host target proteins.

[27059] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM653 gene, herein designated VGAM GENE, on one or more VGAM653 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27060] It is yet further appreciated that a function of VGAM653 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM653 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM653 correlate with, and may be deduced from, the identity of the host target genes which VGAM653 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

- [27061] Nucleotide sequences of the VGAM653 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM653 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM653 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM653 are further described hereinbelow with reference to Table 1.
- [27062] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM653 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM653 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [27063] As mentioned hereinabove with reference to Fig. 1, a function of VGAM653 gene, herein designated VGAM is inhibition of expression of VGAM653 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM653 correlate with, and may be deduced from, the identity of the target genes which VGAM653 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27064] Transient Receptor Potential Cation Channel, Subfamily V, Member 1 (TRPV1, Accession NM\_018727) is a VGAM653 host target gene. TRPV1 BINDING SITE1 through TRPV1 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TRPV1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPV1 BINDING SITE1 through TRPV1 BINDING SITE4, designated SEQ ID:20809, SEQ ID:27989, SEQ ID:27997 and SEQ ID:28005 respectively, to the nucleotide sequence of VGAM653 RNA, herein designated VGAM RNA, also designated SEQ ID:3364.

[27065] A function of VGAM653 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily V, Member 1 (TRPV1, Accession NM\_018727), a gene which functions as a receptor for capsaicin. Accordingly, utilities of VGAM653 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPV1. The function of TRPV1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM146.LOC255147 (Accession XM\_171024) is an-



other VGAM653 host target gene. LOC255147 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255147, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255147 BINDING SITE, designated SEQ ID:45802, to the nucleotide sequence of VGAM653 RNA, herein designated VGAM RNA, also designated SEQ ID:3364.

[27066] Another function of VGAM653 is therefore inhibition of LOC255147 (Accession XM\_171024). Accordingly, utilities of VGAM653 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255147. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 654 (VGAM654) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27067] VGAM654 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM654 was detected is described

hereinabove with reference to Figs. 1–8.

[27068] VGAM654 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM654 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27069] VGAM654 gene encodes a VGAM654 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM654 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM654 precursor RNA is designated SEQ ID:640, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:640 is located at position 75545 relative to the genome of Meleagrid Herpesvirus 1.

[27070] VGAM654 precursor RNA folds onto itself, forming VGAM654 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27071] An enzyme complex designated DICER COMPLEX, `dices` the VGAM654 folded precursor RNA into VGAM654 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 48%) nucleotide sequence of VGAM654 RNA is designated SEQ ID:3365, and is provided hereinbelow with reference to the sequence listing part.

[27072] VGAM654 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM654 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM654 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27073] VGAM654 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM654 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM654 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM654 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM654 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27074] The complementary binding of VGAM654 RNA, herein designated VGAM RNA, to host target binding sites on VGAM654 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM654 host target RNA into VGAM654 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27075] It is appreciated that VGAM654 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM654 host target genes. The mRNA of each one of this plurality of VGAM654 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM654 RNA, herein designated VGAM RNA, and which when bound by VGAM654 RNA causes inhibition of translation of respective one or more VGAM654 host target proteins.

[27076] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM654 gene, herein designated VGAM GENE, on one or more VGAM654 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27077] It is yet further appreciated that a function of VGAM654 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM654 correlate with, and may be deduced from, the identity of the host target genes which VGAM654 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27078] Nucleotide sequences of the VGAM654 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM654 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM654 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM654 are further described hereinbelow with reference to Table 1.

[27079] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM654 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM654 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27080] As mentioned hereinabove with reference to Fig. 1, a function of VGAM654 gene, herein designated VGAM is inhibition of expression of VGAM654 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM654 correlate with, and may be deduced from, the identity of the target genes which VGAM654 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27081] Centrosomal Protein 2 (CEP2, Accession NM\_006779) is a VGAM654 host target gene. CEP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CEP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CEP2 BINDING SITE, designated SEQ ID:13649, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27082] A function of VGAM654 is therefore inhibition of Centrosomal Protein 2 (CEP2, Accession NM\_006779), a gene which interacts with TC10 and CDC42. Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CEP2. The function of CEP2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM329.DKFZP564I052 (Accession XM\_039660) is another VGAM654 host target gene. DKFZP564I052 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564I052, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564I052 BINDING SITE, designated SEQ ID:33138, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also desig-



nated SEQ ID:3365.

[27083] Another function of VGAM654 is therefore inhibition of DKFZP564I052 (Accession XM\_039660). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564I052. Glucocorticoid Modulatory Element Binding Protein 2 (GMEB2, Accession NM\_012384) is another VGAM654 host target gene. GMEB2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GMEB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GMEB2 BINDING SITE, designated SEQ ID:14741, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27084] Another function of VGAM654 is therefore inhibition of Glucocorticoid Modulatory Element Binding Protein 2 (GMEB2, Accession NM\_012384). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GMEB2. KIAA1024 (Accession XM\_044580) is another VGAM654 host target gene. KIAA1024 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by KIAA1024, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1024 BINDING SITE, designated SEQ ID:34232, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27085] Another function of VGAM654 is therefore inhibition of KIAA1024 (Accession XM\_044580). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1024. MGC27434 (Accession NM\_145050) is another VGAM654 host target gene. MGC27434 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC27434, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC27434 BINDING SITE, designated SEQ ID:29681, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27086] Another function of VGAM654 is therefore inhibition of

MGC27434 (Accession NM\_145050). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC27434. Tousled-like Kinase 2 (TLK2, Accession XM\_085650) is another VGAM654 host target gene. TLK2 BINDING SITE1 and TLK2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TLK2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TLK2 BINDING SITE1 and TLK2 BINDING SITE2, designated SEQ ID:38276 and SEQ ID:13722 respectively, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27087] Another function of VGAM654 is therefore inhibition of Tousled-like Kinase 2 (TLK2, Accession XM\_085650). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TLK2. LOC151584 (Accession XM\_098089) is another VGAM654 host target gene. LOC151584 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151584, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151584 BINDING SITE, designated SEQ ID:41377, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27088] Another function of VGAM654 is therefore inhibition of LOC151584 (Accession XM\_098089). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151584. LOC221410 (Accession XM\_166373) is another VGAM654 host target gene. LOC221410 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221410, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221410 BINDING SITE, designated SEQ ID:44196, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27089] Another function of VGAM654 is therefore inhibition of LOC221410 (Accession XM\_166373). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC221410. LOC257249 (Accession XM\_171092) is another VGAM654 host target gene. LOC257249 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257249, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257249 BINDING SITE, designated SEQ ID:45904, to the nucleotide sequence of VGAM654 RNA, herein designated VGAM RNA, also designated SEQ ID:3365.

[27090] Another function of VGAM654 is therefore inhibition of LOC257249 (Accession XM\_171092). Accordingly, utilities of VGAM654 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257249. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 655 (VGAM655) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27091] VGAM655 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM655 was detected is described hereinabove with reference to Figs. 1–8.

[27092] VGAM655 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM655 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27093] VGAM655 gene encodes a VGAM655 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM655 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM655 precursor RNA is designated SEQ ID:641, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:641 is located at position 76605 relative to the genome of Meleagrid Herpesvirus 1.

[27094] VGAM655 precursor RNA folds onto itself, forming VGAM655 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27095] An enzyme complex designated DICER COMPLEX, `dices` the VGAM655 folded precursor RNA into VGAM655 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM655 RNA is designated SEQ ID:3366, and is provided hereinbelow with reference to the sequence listing part.

[27096] VGAM655 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM655 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM655 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27097] VGAM655 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM655 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM655 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM655 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM655 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27098] The complementary binding of VGAM655 RNA, herein



designated VGAM RNA, to host target binding sites on VGAM655 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM655 host target RNA into VGAM655 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27099] It is appreciated that VGAM655 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM655 host target genes. The mRNA of each one of this plurality of VGAM655 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM655 RNA, herein designated VGAM RNA, and which when bound by VGAM655 RNA causes inhibition of translation of respective one or more VGAM655 host target proteins.

[27100] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM655 gene, herein designated VGAM GENE, on one or more VGAM655 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27101] It is yet further appreciated that a function of VGAM655 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM655 correlate with, and may be deduced from, the identity of the host target genes which VGAM655 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27102] Nucleotide sequences of the VGAM655 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM655 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM655 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM655 are further described hereinbelow with reference to Table 1.

[27103] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM655 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM655 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27104] As mentioned hereinabove with reference to Fig. 1, a function of VGAM655 gene, herein designated VGAM is inhibition of expression of VGAM655 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM655 correlate with, and may be deduced from, the identity of the target genes which VGAM655 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27105] Adrenergic, Alpha-2A-, Receptor (ADRA2A, Accession NM\_000681) is a VGAM655 host target gene. ADRA2A BINDING SITE is HOST TARGET binding site found in the

3' untranslated region of mRNA encoded by ADRA2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADRA2A BINDING SITE, designated SEQ ID:6335, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27106] A function of VGAM655 is therefore inhibition of Adrenergic, Alpha-2A-, Receptor (ADRA2A, Accession NM\_000681), a gene which mediates the effects of epinephrine and norepinephrine. Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADRA2A. The function of ADRA2A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM602. Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III) (AGL, Accession NM\_000645) is another VGAM655 host target gene. AGL BINDING SITE1 through AGL BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of

mRNA encoded by AGL, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AGL BINDING SITE1 through AGL BINDING SITE6, designated SEQ ID:6296, SEQ ID:6303, SEQ ID:5464, SEQ ID:6281, SEQ ID:6286 and SEQ ID:6291 respectively, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27107] Another function of VGAM655 is therefore inhibition of Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III) (AGL, Accession NM\_000645). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AGL. Mitogen-activated Protein Kinase 4 (MAPK4, Accession NM\_002747) is another VGAM655 host target gene. MAPK4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAPK4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPK4 BINDING SITE, designated SEQ

ID:8620, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27108] Another function of VGAM655 is therefore inhibition of Mitogen-activated Protein Kinase 4 (MAPK4, Accession NM\_002747), a gene which phosphorylates microtubule-associated protein-2 may promote entry into the cell cycle. Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPK4. The function of MAPK4 has been established by previous studies. See MAPK1 (OMIM Ref. No. 176948). Gonzalez et al. (1992) reported the molecular cloning of genes for 4 human proteins with high homology to members of the mitogen-activated protein kinase group of enzymes. Of the 4, 2 probably resulted from alternative processing of transcripts from a single gene. Zhu et al. (1994) stated that p63MAPK, which had been known as ERK3, shares only 73% protein sequence identity with rat ERK3. They suggested that p97MAPK (MAPK6; 602904) is the true ERK3 homolog, and that p63MAPK is a member of the ERK3 subfamily. Garcia et al. (1996) reported that a gene they referred to as MNK2 is the rat homolog of p63MAPK. The 2 protein se-

quences are 95% identical. Li et al. (1994) used Southern blotting of DNA from a panel of human hamster cell hybrids and fluorescence in situ hybridization to map the MAPK4 gene to 18q12–q21

[27109] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27110] Garcia, J. I.; Zalba, G.; Detera-Wadleigh, S. D.; de Miguel, C. : Isolation of a cDNA encoding the rat MAP–kinase homolog of human p63mapk. Mammalian Genome 7: 810–814, 1996. ; and

[27111] Li, L.; Wylk, M.; Gonzalez, F. A.; Davis, R. J. : Genomic loci of human mitogen–activated protein kinases. Oncogene 9: 647–649, 1994.

[27112] Further studies establishing the function and utilities of MAPK4 are found in John Hopkins OMIM database record ID 176949, and in cited publications numbered 1540–1541, 153 and 1542 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Muscleblind–like (Drosophila) (MBNL, Accession NM\_021038) is another VGAM655 host target gene. MBNL BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MBNL, corre–

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MBNL BINDING SITE, designated SEQ ID:22022, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27113] Another function of VGAM655 is therefore inhibition of Muscleblind-like (Drosophila) (MBNL, Accession NM\_021038), a gene which binds to cug triplet repeat expansion dsrna (by similarity). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBNL. The function of MBNL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM95.Tumor Necrosis Factor (ligand) Superfamily, Member 8 (TNFSF8, Accession NM\_001244) is another VGAM655 host target gene. TNFSF8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFSF8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFSF8 BINDING



SITE, designated SEQ ID:6914, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27114] Another function of VGAM655 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 8 (TNFSF8, Accession NM\_001244), a gene which cytokine that binds to tnfrsf8/cd30. induces proliferation of t cells. Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFSF8. The function of TNFSF8 has been established by previous studies. CD30 (TNFRSF8; 153243), a member of the tumor necrosis factor (TNF; OMIM Ref. No. TNF-alpha 191160) receptor superfamily, is a surface antigen used as a clinical marker for Hodgkin lymphoma and related hematologic malignancies. By performing an expression cloning screen using a chimeric protein containing the extracellular domain of CD30 as a probe, Smith et al. (1993) identified murine cells expressing a CD30 ligand. They isolated the corresponding mouse cDNA and used it to recover a homologous human cDNA from a peripheral blood T-cell (PBT) library. The predicted 234-amino acid human CD30L (CD30 ligand) protein is 72% identical to mouse Cd30l. CD30L has the

characteristics of a type II membrane protein, with no apparent signal peptide and a transmembrane domain followed by a C-terminal extracellular domain. The C-terminal receptor-binding region of CD30L shares sequence similarity with other members of the TNF family, including TNF-alpha, TNF-beta (OMIM Ref. No. 153440), and CD40LG (OMIM Ref. No. 300386). Although it has a predicted molecular weight of 26 kD, recombinant CD30L expressed in mammalian cells migrated at 40 kD by SDS-PAGE. Smith et al. (1993) attributed this discrepancy to extensive glycosylation of the extracellular domain in vivo. The recombinant human CD30L enhanced the proliferation of CD3 (OMIM Ref. No. 186790)-activated T cells, but induced differential responses, including cell death, in several CD30-positive lymphoma-derived cell lines. Northern blot analysis suggested that CD30L expression is limited to specifically induced T cells and monocytes/macrophages. Croager and Abraham (1997) determined that the CD30L gene contains 4 exons and spans more than 17.1 kb. Cerutti et al. (2000) noted that CD153 is expressed on the surface of B cells and found that this expression is upregulated upon CD154 (OMIM Ref. No. CD40LG), IL4 (OMIM Ref. No. 147780), and B-cell receptor

engagement. In these cells, engagement of CD153 by T cell CD30 inhibits immunoglobulin class switch recognition as well as IgG, IgA, and IgE production, suggesting that this 'reverse signaling' modulates the CD154-dependent switching of B cells into the pool producing IgG, IgA, and IgE. By analysis of an interspecific backcross, Smith et al. (1993) mapped the Cd30l gene to the proximal region of mouse chromosome 4. These authors used fluorescence in situ hybridization to map the human CD30L gene to 9q33.

- [27115] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [27116] Cerutti, A.; Schaffer, A.; Goodwin, R. G.; Shah, S.; Zan, H.; Ely, S.; Casali, P. : Engagement of CD153 (CD30 ligand) by CD30-positive T cells inhibits class switch DNA recombination and antibody production in human IgD-positive IgM-positive B cells. *J. Immun.* 165: 786–794, 2000. ; and
- [27117] Croager, E. J.; Abraham, L. J. : Characterisation of the human CD30 ligand gene structure. *Biochim. Biophys. Acta* 1353: 231–235, 1997.
- [27118] Further studies establishing the function and utilities of TNFSF8 are found in John Hopkins OMIM database record

ID 603875, and in cited publications numbered 7602–760 and 7607 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chemokine (C motif) Ligand 1 (XCL1, Accession NM\_002995) is another VGAM655 host target gene. XCL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XCL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XCL1 BINDING SITE, designated SEQ ID:8886, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27119] Another function of VGAM655 is therefore inhibition of Chemokine (C motif) Ligand 1 (XCL1, Accession NM\_002995), a gene which shows chemotactic activity for lymphocytes but not for monocytes or neutrophils. Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XCL1. The function of XCL1 has been established by previous studies. Chemokines are a group of small (approximately 8 to 14 kD), mostly basic, structurally related molecules that regulate cell trafficking of

various types of leukocytes through interactions with a subset of 7-transmembrane G protein-coupled receptors. Chemokines also play fundamental roles in the development, homeostasis, and function of the immune system, and they have effects on cells of the central nervous system as well as on endothelial cells involved in angiogenesis or angiostasis. Chemokines are divided into 2 major subfamilies, CXC and CC, based on the arrangement of the first 2 of the 4 conserved cysteine residues; the 2 cysteines are separated by a single amino acid in CXC chemokines and are adjacent in CC chemokines. By screening a CD8<sup>+</sup> T-lymphocyte cDNA library with a mouse lymphotactin probe, Kennedy et al. (1995) isolated cDNAs encoding the lymphotactin XCL1, later designated SCYC1. The sequence of the deduced 114-amino acid protein is most homologous to the CC chemokines CCL8 and CCL3, but differs in that it lacks the first and third cysteines characteristic of CC and CXC chemokines. By Northern blot analysis, Kennedy et al. (1995) and Yoshida et al. (1995) revealed expression of an 0.8-kb SCYC1 transcript in activated thymic and peripheral blood CD8<sup>+</sup> but not CD4<sup>+</sup> T cells. In normal tissues, SCYC1 is expressed at high levels in spleen, thymus, small intestine,

and peripheral blood leukocytes, as well as at low levels in lung, prostate, and ovary; it shows little or no expression in colon and testis. Lymphotactin is chemotactic for CD4+ and CD8+ T cells but not for monocytes, and induces a rise in intracellular calcium in peripheral blood lymphocytes. Yoshida et al. (1995) and Muller et al. (1995) had identified the same sequence, termed SCM1 and ATAC, respectively, homologous to mouse lymphotactin, but were unable to demonstrate chemotaxis or calcium mobilization.

[27120] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27121] Kennedy, J.; Kelner, G. S.; Kleyensteuber, S.; Schall, T. J.; Weiss, M. C.; Yssel, H.; Schneider, P. V.; Cocks, B. G.; Bacon, K. B.; Zlotnik, A. : Molecular cloning and functional characterization of human lymphotactin. J. Immun. 155: 203–209, 1995. ; and

[27122] Yoshida, T.; Imai, T.; Kakizaki, M.; Nishimura, M.; Yoshie, O. : Molecular cloning of a novel C or gamma type chemokine, SCM–1. FEBS Lett. 360: 155–159, 1995.

[27123] Further studies establishing the function and utilities of XCL1 are found in John Hopkins OMIM database record ID

600250, and in cited publications numbered 7923–7928 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ12056

(Accession NM\_024933) is another VGAM655 host target gene. FLJ12056 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12056 BINDING SITE, designated SEQ ID:24468, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27124] Another function of VGAM655 is therefore inhibition of FLJ12056 (Accession NM\_024933). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12056. HTMP10 (Accession NM\_033207) is another VGAM655 host target gene. HTMP10 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HTMP10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of HTMP10 BINDING SITE, designated SEQ ID:27047, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27125] Another function of VGAM655 is therefore inhibition of HTMP10 (Accession NM\_033207). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTMP10. KIAA0125 (Accession NM\_014792) is another VGAM655 host target gene. KIAA0125 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0125, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0125 BINDING SITE, designated SEQ ID:16687, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27126] Another function of VGAM655 is therefore inhibition of KIAA0125 (Accession NM\_014792). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0125. KIAA0232 (Accession XM\_052627) is another



VGAM655 host target gene. KIAA0232 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0232, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0232 BINDING SITE, designated SEQ ID:36033, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27127] Another function of VGAM655 is therefore inhibition of KIAA0232 (Accession XM\_052627). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0232. KIAA0774 (Accession XM\_166270) is another VGAM655 host target gene. KIAA0774 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0774, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0774 BINDING SITE, designated SEQ ID:44088, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27128] Another function of VGAM655 is therefore inhibition of KIAA0774 (Accession XM\_166270). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0774. KIAA0847 (Accession XM\_085298) is another VGAM655 host target gene. KIAA0847 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0847, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0847 BINDING SITE, designated SEQ ID:38045, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27129] Another function of VGAM655 is therefore inhibition of KIAA0847 (Accession XM\_085298). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0847. SENP7 (Accession NM\_020654) is another VGAM655 host target gene. SENP7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SENP7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SENP7 BINDING SITE, designated SEQ ID:21822, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27130] Another function of VGAM655 is therefore inhibition of SENP7 (Accession NM\_020654). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SENP7. LOC158886 (Accession XM\_096300) is another VGAM655 host target gene. LOC158886 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158886, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158886 BINDING SITE, designated SEQ ID:40311, to the nucleotide sequence of VGAM655 RNA, herein designated VGAM RNA, also designated SEQ ID:3366.

[27131] Another function of VGAM655 is therefore inhibition of LOC158886 (Accession XM\_096300). Accordingly, utilities of VGAM655 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC158886. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 656 (VGAM656) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27132] VGAM656 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM656 was detected is described hereinabove with reference to Figs. 1–8.

[27133] VGAM656 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM656 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27134] VGAM656 gene encodes a VGAM656 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM656 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM656 precursor RNA is designated SEQ ID:642, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:642 is located at position 77387 relative to the genome of Meleagrid Herpesvirus 1.

[27135] VGAM656 precursor RNA folds onto itself, forming VGAM656 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27136] An enzyme complex designated DICER COMPLEX, `dices` the VGAM656 folded precursor RNA into VGAM656 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM656 RNA is designated SEQ ID:3367, and is provided hereinbelow with reference to the sequence listing part.

[27137] VGAM656 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM656 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM656 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27138] VGAM656 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM656 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM656 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM656 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM656 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27139] The complementary binding of VGAM656 RNA, herein designated VGAM RNA, to host target binding sites on VGAM656 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM656 host target RNA into VGAM656 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27140] It is appreciated that VGAM656 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM656 host target genes. The mRNA of each one of this plurality of VGAM656 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM656 RNA, herein designated VGAM RNA, and which when bound by VGAM656 RNA causes in-

hibition of translation of respective one or more VGAM656 host target proteins.

[27141] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM656 gene, herein designated VGAM GENE, on one or more VGAM656 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27142] It is yet further appreciated that a function of VGAM656 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM656 include diagnosis, prevention and



treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM656 correlate with, and may be deduced from, the identity of the host target genes which VGAM656 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [27143] Nucleotide sequences of the VGAM656 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM656 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM656 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM656 are further described hereinbelow with reference to Table 1.
- [27144] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM656 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM656 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [27145] As mentioned hereinabove with reference to Fig. 1, a function of VGAM656 gene, herein designated VGAM is inhibition of expression of VGAM656 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM656 correlate with, and may be deduced from, the identity of the target genes which VGAM656 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27146] Calpain 2, (m/II) Large Subunit (CAPN2, Accession NM\_001748) is a VGAM656 host target gene. CAPN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAPN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAPN2 BINDING SITE, designated SEQ ID:7484, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27147] A function of VGAM656 is therefore inhibition of Calpain 2, (m/II) Large Subunit (CAPN2, Accession NM\_001748). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAPN2. Dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex) (DLST, Accession NM\_001933) is another VGAM656 host target gene. DLST BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by DLST, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLST BINDING SITE, designated SEQ ID:7645, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27148] Another function of VGAM656 is therefore inhibition of Dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex) (DLST, Accession NM\_001933), a gene which catalyzes the oxidative decarboxylation of alpha-keto acids. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLST. The function of DLST has been established by previous studies. The alpha-keto acid dehydrogenase complexes (pyruvate dehydrogenase complex, alpha-ketoglutarate dehydrogenase complex, and branched chain alpha-keto acid dehydrogenase complex) are a family of multienzyme complexes. They are localized in mitochondria and catalyze the oxidative decarboxylation of alpha-keto acids. These 3 alpha-keto acid dehydrogenase complexes are composed of

3 different enzymes: alpha-keto acid dehydrogenase (E1), dihydrolipoamide acyltransferase (E2), and dihydrolipoamide dehydrogenase (E3). Dihydrolipoamide succinyltransferase, which is a component of the structural core of the alpha-keto glutarate dehydrogenase complex, was studied by Nakano et al. (1993), who isolated a cDNA from a human fibroblast cDNA library. They found that the DLST gene contains 3 exons and 4 introns and that the nucleotide sequence at the 5-prime donor and 3-prime acceptor sites of all introns conformed to the gt-ag rule. Amino acid sequences of the 3 exons supported their previous observation (Nakano et al., 1993) that human dihydrolipoamide succinyltransferase lacks a sequence motif for an E1 (OMIM Ref. No. 312170) and/or E3 (OMIM Ref. No. 246900) binding site. By fluorescence in situ hybridization, they found that the DLST gene is located on 14q24.2-q24.3 and that a related sequence is located on 1p31. The gene for the dihydrolipoamide acyltransferase of the branched chain alpha-keto acid dehydrogenase complex (DBT; 248610), the site of the mutation in type 2 maple syrup urine disease, is located on 1p31. Nakano et al. (1993) mentioned the possibility that mutation of the DLST gene may be a cause of familial Alzheimer disease

that maps to 14q24.3 (AD3; 104311). Ali et al. (1994) mapped the DLST gene (symbolized by them KGDHC) to 14q24.3 by isotopic in situ hybridization. The cDNA they used also cross-hybridized to an apparent E2k pseudo-gene on 1p31. Northern analysis demonstrated that the gene is ubiquitously expressed in peripheral tissues and brain. Ali et al. (1994) mentioned Machado-Joseph disease as another candidate for mutation in the DLST gene. DLST is the E2 component of the alpha-ketoglutarate dehydrogenase complex. In contrast to the E2 components of the other 2 alpha-keto acid dehydrogenase complexes, the pyruvate dehydrogenase complex, and the branched-chain alpha-keto acid dehydrogenase complex, the alpha-KGDC E2 has a unique structure consisting of 2 domains and lacking a sequence motif of an E3 and/or E1 binding site (Patel and Harris, 1995).

[27149] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27150] Nakano, K.; Takase, C.; Sakamoto, T.; Ohta, S.; Nakagawa, S.; Ariyama, T.; Inazawa, J.; Abe, T.; Matuda, S. : An unspliced cDNA for human dihydrolipoamide succinyltransferase: characterization and mapping of the gene to chro-

mosome 14q24.2–q24.3. Biochem. Biophys. Res. Commun. 196: 527–533, 1993. ; and

[27151] Patel, M. S.; Harris, R. A. : Mammalian alpha-keto acid dehydrogenase complexes: gene regulation and genetic defects. FASEB J. 9: 1164–1172, 1995.

[27152] Further studies establishing the function and utilities of DLST are found in John Hopkins OMIM database record ID 126063, and in cited publications numbered 4003–4006 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Kelch-like 3 (Drosophila) (KLHL3, Accession XM\_113450) is another VGAM656 host target gene. KLHL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KLHL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KLHL3 BINDING SITE, designated SEQ ID:42267, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27153] Another function of VGAM656 is therefore inhibition of Kelch-like 3 (Drosophila) (KLHL3, Accession XM\_113450). Accordingly, utilities of VGAM656 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with KLHL3. LanC Lantibiotic Synthetase Component C-like 1 (bacterial) (LANCL1, Accession NM\_006055) is another VGAM656 host target gene.

LANCL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LANCL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LANCL1 BINDING SITE, designated SEQ ID:12696, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27154] Another function of VGAM656 is therefore inhibition of LanC Lantibiotic Synthetase Component C-like 1 (bacterial) (LANCL1, Accession NM\_006055), a gene which binds the C-terminus of stomatin. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LANCL1. The function of LANCL1 has been established by previous studies. By affinity chromatography of solubilized human erythrocyte membrane proteins, Mayer et al. (1998) identified p40, a 40-kD protein that interacts with the C-

terminus of the membrane protein stomatin (OMIM Ref. No. 133090). They used the sequence of p40 peptides to identify partial cDNAs in an EST database, and then cloned cDNAs corresponding to the entire coding region using a PCR strategy. The predicted 399-amino acid protein contains the characteristic features of G protein-coupled receptors (GPCRs), including 7 transmembrane domains. Northern blot analysis revealed that p40 is expressed as a major 4.8-kb mRNA and as a minor 1.9-kb mRNA in all tissues. Dot blot experiments indicated that the highest levels of expression were in brain, spinal cord, testis, pituitary gland, and kidney. Using in situ hybridization to monkey tissues, Mayer et al. (1998) determined that p40 is expressed at high levels in neurons of the brain and spinal cord, in thymocytes, megakaryocytes, and macrophages. Bauer et al. (2000) determined that LANCL1 is not an integral membrane protein, but rather a weakly associated peripheral membrane protein, and is not a GPCR. They found that LANCL1 contains 7 highly conserved hydrophobic repeats and may play a role in peptide modification. Western blot analysis showed that LANCL1 is mainly expressed in brain, testis, ovary, and kidney. Mayer et al. (2001) determined that the human and mouse



LANCL1 genes span 45 kb and 38 kb, respectively, each comprising 10 exons

[27155] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27156] Bauer, H.; Mayer, H.; Marchler-Bauer, A.; Salzer, U.; Prohaska, R. : Characterization of p40/GPR69A as a peripheral membrane protein related to the lantibiotic synthetase component C. *Biochem. Biophys. Res. Commun.* 275: 69–74, 2000. ; and

[27157] Mayer, H.; Bauer, H.; Prohaska, R. : Organization and chromosomal localization of the human and mouse genes coding for LanC-like protein 1 (LANCL1). *Cytogenet. Cell Genet.* 93: 100–104.

[27158] Further studies establishing the function and utilities of LANCL1 are found in John Hopkins OMIM database record ID 604155, and in cited publications numbered 417–419 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Mesoderm Specific Transcript Homolog (mouse) (MEST, Accession XM\_046001) is another VGAM656 host target gene. MEST BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MEST, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEST BINDING SITE, designated SEQ ID:34639, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27159] Another function of VGAM656 is therefore inhibition of Mesoderm Specific Transcript Homolog (mouse) (MEST, Accession XM\_046001), a gene which appears to be required for the appropriate immediate response of females to their pups. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEST. The function of MEST has been established by previous studies. The Mest gene maps to an imprinted region of mouse chromosome 6 and is expressed monoallelically from the paternal allele. When the null allele is paternally transmitted, the offspring exhibits severe intrauterine growth retardation. Uniparental disomy of mouse chromosome 6 is associated with a similar phenotype, presumably as a result of lack of expression of the Mest gene (Ferguson-Smith et al., 1991). The human homolog, MEST, maps to 7q31.3, within a region of conserved synteny corresponding to

mouse chromosome 6, and is monoallelically expressed from the paternal allele in a wide variety of tissues during prenatal and postnatal development. Uniparental disomy of chromosome 7 in humans is associated with phenotypic features of Silver–Russell syndrome (SRS; 180860), a heterogeneous disorder characterized by intrauterine and postnatal growth retardation, with or without additional dysmorphic features. Kotzot et al. (1995) predicted the presence of at least one maternally repressed gene on human chromosome 7, because they found maternal uniparental disomy for this chromosome in 4 of 35 patients with SRS. Nishita et al. (1996) suggested that MEST, the first imprinted gene to be identified on chromosome 7, is involved in the causation of this syndrome. Riesewijk et al. (1998) performed a mutation screen of the PEG1/MEST gene in 49 patients with SRS and 9 patients with primordial growth retardation (PGR). As background for this, they determined the complete genomic structure of the MEST gene, which comprises 12 exons. Apart from 1 silent mutation and 2 novel polymorphisms, nucleotide changes were not detected in any of the SRS or PGR patients. Moreover, methylation patterns of the 5–prime region of PEG1/MEST were found to be normal in 35 SRS and 9 PGR

patients and different from the pattern seen in patients with maternal uniparental disomy 7. Kobayashi et al. (2001) presented findings indicating that PEG1/MEST can be excluded as a major determinant of SRS. In a screening of 15 SRS patients, no aberrant expression patterns of 2 splice variants were detected in lymphocytes. Direct sequence analysis failed to detect any mutations in the coding region of isoform-1, which the authors called alpha, and there were no significant mutations in the 5-prime flanking upstream region containing the predicted promoter and the genomic region that is highly conserved between human and mouse. Differential methylation patterns of the CpG islands for the alpha isoform were normally maintained and resulted in the same patterns as in normal controls, suggesting that there was no loss of imprinting.

[27160] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27161] Nishita, Y.; Yoshida, I.; Sado, T.; Takagi, N. : Genomic imprinting and chromosomal localization of the human MEST gene. Genomics 36: 539–542, 1996. ; and

[27162] Kobayashi, S.; Uemura, H.; Kohda, T.; Nagai, T.; Chinen,

Y.; Naritomi, K.; Kinoshita, E.; Ohashi, H.; Imaizumi, K.; Tsukahara, M.; Sugio, Y.; Tonoki, H.; Kishino, T.; Tanaka, T.; Yamada, M.

[27163] Further studies establishing the function and utilities of MEST are found in John Hopkins OMIM database record ID 601029, and in cited publications numbered 4307, 9967–9968, 9332, 9969–9972, 1024 and 10675–10677 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Myosin X (MYO10, Accession NM\_012334) is another VGAM656 host target gene. MYO10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYO10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYO10 BINDING SITE, designated SEQ ID:14732, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27164] Another function of VGAM656 is therefore inhibition of Myosin X (MYO10, Accession NM\_012334), a gene which is an unconventional myosin. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with MYO10. The function of MYO10 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM28. Polymeric Immunoglobulin Receptor (PIGR, Accession XM\_052013) is another VGAM656 host target gene. PIGR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIGR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIGR BINDING SITE, designated SEQ ID:35937, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27165] Another function of VGAM656 is therefore inhibition of Polymeric Immunoglobulin Receptor (PIGR, Accession XM\_052013). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIGR. Pleckstrin Homology, Sec7 and Coiled/coil Domains 4 (PSCD4, Accession NM\_013385) is another VGAM656 host target gene. PSCD4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PSCD4,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSCD4 BINDING SITE, designated SEQ ID:15035, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27166] Another function of VGAM656 is therefore inhibition of Pleckstrin Homology, Sec7 and Coiled/coil Domains 4 (PSCD4, Accession NM\_013385), a gene which promotes guanine-nucleotide exchange on arf1 and arf5. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSCD4. The function of PSCD4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM615. Solute Carrier Family 16 (monocarboxylic acid transporters), Member 2 (putative transporter) (SLC16A2, Accession NM\_006517) is another VGAM656 host target gene. SLC16A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC16A2, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC16A2 BINDING SITE, designated SEQ ID:13271, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27167] Another function of VGAM656 is therefore inhibition of Solute Carrier Family 16 (monocarboxylic acid transporters), Member 2 (putative transporter) (SLC16A2, Accession NM\_006517). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC16A2. Stress 70 Protein Chaperone, Microsome-associated, 60kDa (STCH, Accession NM\_006948) is another VGAM656 host target gene. STCH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STCH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STCH BINDING SITE, designated SEQ ID:13835, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27168] Another function of VGAM656 is therefore inhibition of Stress 70 Protein Chaperone, Microsome-associated,



60kDa (STCH, Accession NM\_006948), a gene which has peptide-independent atpase activity. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STCH. The function of STCH and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM550. Sulfotransferase Family, Cytosolic, 1C, Member 1 (SULT1C1, Accession NM\_001056) is another VGAM656 host target gene. SULT1C1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SULT1C1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SULT1C1 BINDING SITE, designated SEQ ID:6722, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27169] Another function of VGAM656 is therefore inhibition of Sulfotransferase Family, Cytosolic, 1C, Member 1 (SULT1C1, Accession NM\_001056). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SULT1C1.

Thiamin Pyrophosphokinase 1 (TPK1, Accession NM\_022445) is another VGAM656 host target gene. TPK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TPK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TPK1 BINDING SITE, designated SEQ ID:22781, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27170] Another function of VGAM656 is therefore inhibition of Thiamin Pyrophosphokinase 1 (TPK1, Accession NM\_022445), a gene which catalyzes the conversion of thiamine, a form of vitamin B1, to thiamine pyrophosphate . Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TPK1. The function of TPK1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM475. Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase Activation Protein, Epsilon Polypeptide (YWHAE, Accession NM\_006761) is another VGAM656 host target gene.

YWHAЕ BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by YWHAЕ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of YWHAЕ BINDING SITE, designated SEQ ID:13612, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27171] Another function of VGAM656 is therefore inhibition of Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase Activation Protein, Epsilon Polypeptide (YWHAЕ, Accession NM\_006761), a gene which binds to cdc25 and may facilitate cdc25 interaction with Raf-1 in vivo. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with YWHAЕ. The function of YWHAЕ has been established by previous studies. Using a yeast 2-hybrid screen to probe a HeLa cell library with CDC25A (OMIM Ref. No. 116947) and CDC25B (OMIM Ref. No. 116949) as bait, Conklin et al. (1995) isolated cDNAs encoding YWHAB (OMIM Ref. No. 601289), which they called 14-3-3-beta, and YWHAЕ, which they called

14-3-3-epsilon. YWHAE encodes a deduced 260-amino acid protein that is 100% identical to the mouse sequence. Both 14-3-3 proteins interacted with either CDC protein but did not affect their phosphatase activities. Like YWHAB, YWHAE interacted with RAF1 (OMIM Ref. No. 164760) but not RAS (OMIM Ref. No. 190020) in yeast 2-hybrid screens and may facilitate the association of CDC25 with RAF1. The binding of insulin (OMIM Ref. No. 176730) to its receptor induces the phosphorylation of the cytosolic substrates IRS1 (OMIM Ref. No. 147545) and IRS2 (OMIM Ref. No. 600797), which associate with several Src homology-2 (SH2) domain-containing proteins. To identify unique IRS1-binding proteins, Ogihara et al. (1997) screened a human heart cDNA expression library with recombinant IRS1. They obtained 2 isoforms of the 14-3-3 protein family, 14-3-3-zeta (YWHAZ; 601288) and -epsilon. 14-3-3 protein has been shown to associate with IRS1 in L6 myotubes, HepG2 hepatoma cells, Chinese hamster ovary cells, and bovine brain tissue. IRS2, a protein structurally similar to IRS1, was also shown to form a complex with 14-3-3 protein using a baculovirus expression system. The amount of 14-3-3 protein associated with IRS1 was not affected by insulin stimulation but

was increased significantly by treatment with okadaic acid, a potent serine/threonine phosphatase inhibitor. The authors identified a putative 14-3-3 protein-binding site within the phosphotyrosine-binding (PTB) domain of IRS1. Ogihara et al. (1997) suggested that the association with 14-3-3 protein may play a role in the regulation of insulin sensitivity by interrupting the association between the insulin receptor and IRS1.

[27172] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27173] Conklin, D. S.; Galaktionov, K.; Beach, D. : 14-3-3 proteins associate with cdc25 phosphatases. Proc. Nat. Acad. Sci. 92: 7892-7896, 1995. ; and

[27174] Ogihara, T.; Isobe, T.; Ichimura, T.; Taoka, M.; Funaki, M.; Sakoda, H.; Onishi, Y.; Inukai, K.; Anai, M.; Fukushima, Y.; Kikuchi, M.; Yazaki, Y.; Oka, Y.; Asano, T. : 14-3-3 protein bin.

[27175] Further studies establishing the function and utilities of YWHAЕ are found in John Hopkins OMIM database record ID 605066, and in cited publications numbered 6799-6800, 10093-680 and 4469 listed in the bibliography section hereinbelow, which are also hereby incorpo-

rated by reference. Zinc Finger Protein 144 (Mel-18) (ZNF144, Accession NM\_007144) is another VGAM656 host target gene. ZNF144 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF144, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF144 BINDING SITE, designated SEQ ID:13989, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27176] Another function of VGAM656 is therefore inhibition of Zinc Finger Protein 144 (Mel-18) (ZNF144, Accession NM\_007144), a gene which is a transcriptional repressor and may play a role in the control of cell proliferation. Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF144. The function of ZNF144 and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM380. Apolipoprotein L, 4 (APOL4, Accession NM\_030643) is another VGAM656 host target gene. APOL4 BINDING SITE is HOST TARGET binding

site found in the 5` untranslated region of mRNA encoded by APOL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APOL4 BINDING SITE, designated SEQ ID:24977, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27177] Another function of VGAM656 is therefore inhibition of Apolipoprotein L, 4 (APOL4, Accession NM\_030643). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOL4. Chromosome 20 Open Reading Frame 30 (C20orf30, Accession NM\_014145) is another VGAM656 host target gene. C20orf30 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C20orf30, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf30 BINDING SITE, designated SEQ ID:15432, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27178] Another function of VGAM656 is therefore inhibition of Chromosome 20 Open Reading Frame 30 (C20orf30, Accession NM\_014145). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf30.

FLJ12985 (Accession NM\_024924) is another VGAM656 host target gene. FLJ12985 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12985, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12985 BINDING SITE, designated SEQ ID:24462, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27179] Another function of VGAM656 is therefore inhibition of FLJ12985 (Accession NM\_024924). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12985. KIAA0179 (Accession XM\_035973) is another VGAM656 host target gene. KIAA0179 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0179, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0179 BINDING SITE, designated SEQ ID:32364, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27180] Another function of VGAM656 is therefore inhibition of KIAA0179 (Accession XM\_035973). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0179. KIAA1877 (Accession XM\_038616) is another VGAM656 host target gene. KIAA1877 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1877, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1877 BINDING SITE, designated SEQ ID:32878, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27181] Another function of VGAM656 is therefore inhibition of KIAA1877 (Accession XM\_038616). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1877. PRO0767 (Accession NM\_014083) is another VGAM656 host target gene. PRO0767 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO0767, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0767 BINDING SITE, designated SEQ ID:15309, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27182] Another function of VGAM656 is therefore inhibition of PRO0767 (Accession NM\_014083). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0767. Serine Protease Inhibitor-like, with Kunitz and WAP Domains 1 (eppin) (SPINLW1, Accession NM\_020398) is another VGAM656 host target gene. SPINLW1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPINLW1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPINLW1

BINDING SITE, designated SEQ ID:21665, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27183] Another function of VGAM656 is therefore inhibition of Serine Protease Inhibitor-like, with Kunitz and WAP Domains 1 (eppin) (SPINLW1, Accession NM\_020398). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPINLW1. LOC138307 (Accession XM\_059963) is another VGAM656 host target gene. LOC138307 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC138307, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC138307 BINDING SITE, designated SEQ ID:37122, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27184] Another function of VGAM656 is therefore inhibition of LOC138307 (Accession XM\_059963). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC138307. LOC144182 (Accession NM\_139136) is another VGAM656 host target gene. LOC144182 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144182, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144182 BINDING SITE, designated SEQ ID:29166, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27185] Another function of VGAM656 is therefore inhibition of LOC144182 (Accession NM\_139136). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144182. LOC149734 (Accession XM\_097713) is another VGAM656 host target gene. LOC149734 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149734, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149734 BINDING SITE, designated SEQ ID:41054, to the nucleotide sequence of VGAM656 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3367.

[27186] Another function of VGAM656 is therefore inhibition of LOC149734 (Accession XM\_097713). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149734. LOC157983 (Accession XM\_088433) is another VGAM656 host target gene. LOC157983 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157983, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157983 BINDING SITE, designated SEQ ID:39687, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27187] Another function of VGAM656 is therefore inhibition of LOC157983 (Accession XM\_088433). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157983. LOC158857 (Accession XM\_098997) is another VGAM656 host target gene. LOC158857 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158857, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158857 BINDING SITE, designated SEQ ID:42030, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27188] Another function of VGAM656 is therefore inhibition of LOC158857 (Accession XM\_098997). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158857. LOC159049 (Accession XM\_099020) is another VGAM656 host target gene. LOC159049 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC159049, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC159049 BINDING SITE, designated SEQ ID:42056, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27189] Another function of VGAM656 is therefore inhibition of LOC159049 (Accession XM\_099020). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC159049. LOC168283 (Accession XM\_094966) is another VGAM656 host target gene. LOC168283 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC168283, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC168283 BINDING SITE, designated SEQ ID:40240, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27190] Another function of VGAM656 is therefore inhibition of LOC168283 (Accession XM\_094966). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC168283. LOC203289 (Accession XM\_114672) is another VGAM656 host target gene. LOC203289 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC203289, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203289 BINDING SITE, designated SEQ ID:43029, to

the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27191] Another function of VGAM656 is therefore inhibition of LOC203289 (Accession XM\_114672). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203289. LOC203378 (Accession XM\_117541) is another VGAM656 host target gene. LOC203378 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC203378, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203378 BINDING SITE, designated SEQ ID:43545, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27192] Another function of VGAM656 is therefore inhibition of LOC203378 (Accession XM\_117541). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203378. LOC255624 (Accession XM\_170531) is another VGAM656 host target gene. LOC255624 BINDING SITE is HOST TARGET binding site found in the 3` un-



translated region of mRNA encoded by LOC255624, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255624 BINDING SITE, designated SEQ ID:45350, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27193] Another function of VGAM656 is therefore inhibition of LOC255624 (Accession XM\_170531). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255624. LOC256544 (Accession XM\_171228) is another VGAM656 host target gene. LOC256544 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC256544, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256544 BINDING SITE, designated SEQ ID:46016, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27194] Another function of VGAM656 is therefore inhibition of LOC256544 (Accession XM\_171228). Accordingly, utilities

of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256544. LOC91151 (Accession NM\_033208) is another VGAM656 host target gene. LOC91151 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC91151, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91151 BINDING SITE, designated SEQ ID:27052, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27195] Another function of VGAM656 is therefore inhibition of LOC91151 (Accession NM\_033208). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91151. LOC92492 (Accession XM\_045396) is another VGAM656 host target gene. LOC92492 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC92492, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC92492 BINDING SITE, designated SEQ ID:34454, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27196] Another function of VGAM656 is therefore inhibition of LOC92492 (Accession XM\_045396). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92492. LOC92573 (Accession XM\_045884) is another VGAM656 host target gene. LOC92573 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92573, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92573 BINDING SITE, designated SEQ ID:34594, to the nucleotide sequence of VGAM656 RNA, herein designated VGAM RNA, also designated SEQ ID:3367.

[27197] Another function of VGAM656 is therefore inhibition of LOC92573 (Accession XM\_045884). Accordingly, utilities of VGAM656 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92573. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 657 (VGAM657) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27198] VGAM657 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM657 was detected is described hereinabove with reference to Figs. 1–8.

[27199] VGAM657 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM657 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27200] VGAM657 gene encodes a VGAM657 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM657 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM657 precursor RNA is designated SEQ ID:643, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:643 is located at position 75089 relative to the genome of Me–

leagrid Herpesvirus 1.

[27201] VGAM657 precursor RNA folds onto itself, forming VGAM657 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27202] An enzyme complex designated DICER COMPLEX, `dices` the VGAM657 folded precursor RNA into VGAM657 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM657 RNA is designated SEQ ID:3368, and is provided hereinbelow with reference to the sequence listing part.

[27203] VGAM657 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM657 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM657 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27204] VGAM657 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM657 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM657 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM657 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM657 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27205] The complementary binding of VGAM657 RNA, herein designated VGAM RNA, to host target binding sites on VGAM657 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM657 host target RNA into VGAM657 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27206] It is appreciated that VGAM657 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM657 host target genes. The mRNA of each one of this plurality of VGAM657 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM657 RNA, herein designated VGAM RNA, and which when bound by VGAM657 RNA causes inhibition of translation of respective one or more VGAM657 host target proteins.

[27207] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM657 gene, herein designated VGAM GENE, on one or more VGAM657 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27208] It is yet further appreciated that a function of VGAM657 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM657



correlate with, and may be deduced from, the identity of the host target genes which VGAM657 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27209] Nucleotide sequences of the VGAM657 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM657 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM657 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM657 are further described hereinbelow with reference to Table 1.

[27210] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM657 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM657 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27211] As mentioned hereinabove with reference to Fig. 1, a function of VGAM657 gene, herein designated VGAM is inhibition of expression of VGAM657 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM657 correlate with, and may be deduced

from, the identity of the target genes which VGAM657 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27212] LanC Lantibiotic Synthetase Component C-like 1 (bacterial) (LANCL1, Accession NM\_006055) is a VGAM657 host target gene. LANCL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LANCL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LANCL1 BINDING SITE, designated SEQ ID:12694, to the nucleotide sequence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27213] A function of VGAM657 is therefore inhibition of LanC Lantibiotic Synthetase Component C-like 1 (bacterial) (LANCL1, Accession NM\_006055), a gene which binds the C-terminus of stomatin. Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LANCL1. The function of LANCL1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM656.Family with Sequence Similarity 8, Member A1 (FAM8A1, Accession NM\_016255) is another VGAM657 host target gene. FAM8A1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FAM8A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FAM8A1 BINDING SITE, designated SEQ ID:18381, to the nucleotide sequence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27214] Another function of VGAM657 is therefore inhibition of Family with Sequence Similarity 8, Member A1 (FAM8A1, Accession NM\_016255). Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FAM8A1. Origin Recognition Complex, Subunit 6 Homolog-like (yeast) (ORC6L, Accession NM\_014321) is another VGAM657 host target gene. ORC6L BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ORC6L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of ORC6L BINDING SITE, designated SEQ ID:15620, to the nucleotide sequence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27215] Another function of VGAM657 is therefore inhibition of Origin Recognition Complex, Subunit 6 Homolog-like (yeast) (ORC6L, Accession NM\_014321). Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ORC6L. Serine/threonine Kinase 38 Like (STK38L, Accession XM\_044823) is another VGAM657 host target gene. STK38L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STK38L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STK38L BINDING SITE, designated SEQ ID:34291, to the nucleotide sequence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27216] Another function of VGAM657 is therefore inhibition of Serine/threonine Kinase 38 Like (STK38L, Accession XM\_044823). Accordingly, utilities of VGAM657 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with STK38L. ZER6 (Accession XM\_032742) is another VGAM657 host target gene. ZER6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZER6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZER6 BINDING SITE, designated SEQ ID:31741, to the nucleotide sequence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27217] Another function of VGAM657 is therefore inhibition of ZER6 (Accession XM\_032742). Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZER6. Zinc Finger RNA Binding Protein (ZFR, Accession NM\_016107) is another VGAM657 host target gene. ZFR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZFR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFR BINDING SITE, designated SEQ ID:18187, to the nucleotide se-

quence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27218] Another function of VGAM657 is therefore inhibition of Zinc Finger RNA Binding Protein (ZFR, Accession NM\_016107). Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFR. LOC152765 (Accession XM\_087519) is another VGAM657 host target gene. LOC152765 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152765, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152765 BINDING SITE, designated SEQ ID:39317, to the nucleotide sequence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27219] Another function of VGAM657 is therefore inhibition of LOC152765 (Accession XM\_087519). Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152765. LOC256401 (Accession XM\_171149) is another VGAM657 host target gene. LOC256401 BINDING

SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256401, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256401 BINDING SITE, designated SEQ ID:45946, to the nucleotide sequence of VGAM657 RNA, herein designated VGAM RNA, also designated SEQ ID:3368.

[27220] Another function of VGAM657 is therefore inhibition of LOC256401 (Accession XM\_171149). Accordingly, utilities of VGAM657 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256401. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 658 (VGAM658) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27221] VGAM658 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM658 was detected is described hereinabove with reference to Figs. 1-8.

[27222] VGAM658 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM658 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27223] VGAM658 gene encodes a VGAM658 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM658 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM658 precursor RNA is designated SEQ ID:644, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:644 is located at position 79923 relative to the genome of Meleagrid Herpesvirus 1.

[27224] VGAM658 precursor RNA folds onto itself, forming VGAM658 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-



cleotide sequence of the second half thereof.

[27225] An enzyme complex designated DICER COMPLEX, `dices` the VGAM658 folded precursor RNA into VGAM658 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM658 RNA is designated SEQ ID:3369, and is provided hereinbelow with reference to the sequence listing part.

[27226] VGAM658 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM658 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM658 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27227] VGAM658 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM658 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM658 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM658 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM658 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27228] The complementary binding of VGAM658 RNA, herein designated VGAM RNA, to host target binding sites on VGAM658 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM658 host target RNA into VGAM658 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27229] It is appreciated that VGAM658 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM658 host target genes. The mRNA of each one of this plurality of VGAM658 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM658 RNA, herein designated VGAM RNA, and which when bound by VGAM658 RNA causes inhibition of translation of respective one or more VGAM658 host target proteins.

[27230] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM658 gene, herein designated VGAM GENE, on one or more VGAM658 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27231] It is yet further appreciated that a function of VGAM658 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM658 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM658 correlate with, and may be deduced from, the identity of the host target genes which VGAM658 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27232] Nucleotide sequences of the VGAM658 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM658 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM658 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM658 are further described hereinbelow with reference to Table 1.

[27233] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM658 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM658 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27234] As mentioned hereinabove with reference to Fig. 1, a function of VGAM658 gene, herein designated VGAM is inhibition of expression of VGAM658 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM658 correlate with, and may be deduced from, the identity of the target genes which VGAM658 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27235] CMG2 (Accession NM\_058172) is a VGAM658 host target gene. CMG2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CMG2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of CMG2 BINDING SITE, designated SEQ ID:27716, to the nucleotide sequence of VGAM658 RNA, herein designated VGAM RNA, also designated SEQ ID:3369.

[27236] A function of VGAM658 is therefore inhibition of CMG2 (Accession NM\_058172). Accordingly, utilities of VGAM658 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CMG2. LOC91664 (Accession XM\_039908) is another VGAM658 host target gene. LOC91664 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91664, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91664 BINDING SITE, designated SEQ ID:33214, to the nucleotide sequence of VGAM658 RNA, herein designated VGAM RNA, also designated SEQ ID:3369.

[27237] Another function of VGAM658 is therefore inhibition of LOC91664 (Accession XM\_039908). Accordingly, utilities of VGAM658 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91664. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 659 (VGAM659) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27238] VGAM659 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM659 was detected is described hereinabove with reference to Figs. 1–8.

[27239] VGAM659 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM659 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27240] VGAM659 gene encodes a VGAM659 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM659 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM659 precursor RNA is designated SEQ ID:645, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:645 is

located at position 80037 relative to the genome of Meleagrid Herpesvirus 1.

[27241] VGAM659 precursor RNA folds onto itself, forming VGAM659 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27242] An enzyme complex designated DICER COMPLEX, `dices` the VGAM659 folded precursor RNA into VGAM659 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 57%) nucleotide sequence of VGAM659 RNA is designated SEQ ID:3370, and is provided hereinbelow with reference to the sequence listing part.

[27243] VGAM659 host target gene, herein designated VGAM



HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM659 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM659 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[27244] VGAM659 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM659 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM659 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM659 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM659 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27245] The complementary binding of VGAM659 RNA, herein designated VGAM RNA, to host target binding sites on VGAM659 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM659 host target RNA into VGAM659 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27246] It is appreciated that VGAM659 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM659 host target genes. The mRNA of each one of this plurality of VGAM659 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM659 RNA, herein designated VGAM RNA, and which when bound by VGAM659 RNA causes inhibition of translation of respective one or more VGAM659

host target proteins.

[27247] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM659 gene, herein designated VGAM GENE, on one or more VGAM659 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27248] It is yet further appreciated that a function of VGAM659 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1.

Specific functions, and accordingly utilities, of VGAM659 correlate with, and may be deduced from, the identity of the host target genes which VGAM659 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27249] Nucleotide sequences of the VGAM659 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM659 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM659 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM659 are further described hereinbelow with reference to Table 1.

[27250] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM659 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM659 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27251] As mentioned hereinabove with reference to Fig. 1, a function of VGAM659 gene, herein designated VGAM is inhibition of expression of VGAM659 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM659 correlate with, and may be deduced from, the identity of the target genes which VGAM659 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27252] ATPase, Na<sup>+</sup>/K<sup>+</sup> Transporting, Beta 2 Polypeptide (ATP1B2, Accession NM\_001678) is a VGAM659 host target gene. ATP1B2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP1B2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP1B2 BINDING SITE, designated SEQ ID:7389, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27253] A function of VGAM659 is therefore inhibition of ATPase, Na<sup>+</sup>/K<sup>+</sup> Transporting, Beta 2 Polypeptide (ATP1B2, Accession NM\_001678), a gene which catalyzes the hydrolysis of ATP coupled with the exchange of Na<sup>+</sup>/K<sup>+</sup> ions across the plasma membrane. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP1B2. The function of ATP1B2 and its association with various

diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152.Disabled Homolog 2, Mitogen-responsive Phosphoprotein (Drosophila) (DAB2, Accession NM\_001343) is another VGAM659 host target gene. DAB2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DAB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAB2 BINDING SITE, designated SEQ ID:7021, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27254] Another function of VGAM659 is therefore inhibition of Disabled Homolog 2, Mitogen-responsive Phosphoprotein (Drosophila) (DAB2, Accession NM\_001343), a gene which may be a component of the csf-1 signal transduction pathway. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAB2. The function of DAB2 has been established by previous studies. Mok et al. (1994) used a PCR-based differential display method to identify genes expressed in ovarian cancer. Two cDNAs,

termed DOC1 and DOC2 by them (for Differentially expressed in Ovarian Cancer), were identified that were expressed in normal ovarian epithelial cells but were down-regulated or absent from ovarian carcinoma cell lines. Albertsen et al. (1996) determined the complete sequence of the 3.2-kb DOC2 cDNA. They also cloned a genomic fragment at the 5-prime end of the gene which includes exons 1 to 8. The 770-amino acid predicted protein has an overall 83% identity with the mouse p96 protein, a putative mitogen-responsive phosphoprotein; homology is strongest in the amino-terminal end of the protein in a region corresponding to the phosphotyrosine interaction domain. The mouse p96 protein is phosphorylated on serine residues rather than tyrosines; phosphorylation is lowest in the G1 cell cycle stage but rapidly increases following mitogenic stimulation with colony stimulating factor (OMIM Ref. No. 120420)(Xu et al., 1995). Albertsen et al. (1996) mapped the DOC2 gene to 5p13 by fluorescence in situ hybridization and confirmed the mapping through analysis of a human/rodent somatic cell hybrid mapping panel. The authors stated that DOC2 is expressed in at least 7 different human tissues and that it and its murine homolog are likely expressed in a tissue-

independent manner. Mok et al. (1998) reported that when DOC2 was transfected into an ovarian carcinoma cell line, the stable transfectants showed significantly reduced growth rate and ability to form tumors in nude mice.

[27255] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27256] Mok, S. C.; Chan, W. Y.; Wong, K. K.; Cheung, K. K.; Lau, C. C.; Ng, S. W.; Baldini, A.; Colitti, C. V.; Rock, C. O.; Berkowitz, R. S. : DOC-2, a candidate tumor suppressor gene in human epithelial ovarian cancer. *Oncogene* 16: 2381-2387, 1998. ; and

[27257] Xu, X.-X.; Yang, W.; Jackowski, S.; Rock, C. O. : Cloning of a novel phosphoprotein regulated by colony-stimulating factor 1 shares a domain with the *Drosophila* disabled gene product. *J.*

[27258] Further studies establishing the function and utilities of DAB2 are found in John Hopkins OMIM database record ID 601236, and in cited publications numbered 2837-283 and 2827-2828 listed in the bibliography section herein-below, which are also hereby incorporated by reference. Potassium Voltage-gated Channel, Shaker-related Subfamily, Beta Member 2 (KCNA2, Accession



NM\_003636) is another VGAM659 host target gene. KCNAB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNAB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNAB2 BINDING SITE, designated SEQ ID:9704, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27259] Another function of VGAM659 is therefore inhibition of Potassium Voltage-gated Channel, Shaker-related Subfamily, Beta Member 2 (KCNAB2, Accession NM\_003636), a gene which is the beta subunit of shaker voltage-gated potassium channels. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNAB2. The function of KCNAB2 has been established by previous studies. 'Shaker' and other voltage-dependent potassium channel proteins help to determine the electrical properties of excitable cells and play additional physiologic roles in nonexcitable cell types. See KCNA1 (OMIM Ref. No. 176260). Mammalian Shaker potassium channel alpha

subunits associate with cytoplasmic beta subunits that modulate the inactivation of the channel. The beta subunits belong to a superfamily of NAD(P)H-dependent enzymes, suggesting that they may be involved in additional physiologic processes. Shaker potassium channel complexes are thought to be composed of 4 alpha and 4 beta subunits. By PCR of a human hippocampal library with degenerate primers based on conserved regions of rat beta-1 (KCNA1B; 601141) and beta-2 subunits, McCormack et al. (1995) isolated cDNAs encoding human beta-1 and beta-2. The predicted 367-amino acid human, bovine, and rat beta-2 subunits are 99% identical. Unlike beta-1, the beta-2 subunit does not contain an N-terminal inactivation 'ball' domain. Instead, functional studies of beta-2 expressed in *Xenopus* oocytes indicated that it increased the rate of the endogenous Kv1.4 alpha subunit (OMIM Ref. No. 176266) inactivation process. Leicher et al. (1998) reported that the KCNA2B gene contains 15 exons and spans approximately 70 kb. The exon/intron structure of KCNA2B is comparable to that of KCNA1B and KCNA3B (OMIM Ref. No. 604111), although the size of the introns varies significantly among the genes. By analysis of somatic cell hybrids and by FISH, Schultz et al. (1996)

mapped the KCNA2B gene to 1p36.3. The results of Gong et al. (1999) suggested that ZIP, the rat homolog of p62 (OMIM Ref. No. 601530), acts as a link that targets the activity of Kv-beta-2 and PKC-zeta

[27260] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27261] Gong, J.; Xu, J.; Bezanilla, M.; van Huizen, R.; Derin, R.; Li, M. : Differential stimulation of PKC phosphorylation of potassium channels by ZIP1 and ZIP2. Science 285: 1565–1569, 1999. ; and

[27262] Leicher, T.; Bähring, R.; Isbrandt, D.; Pongs, O. : Coexpression of the KCNA3B gene product with Kv1.5 leads to a novel A-type potassium channel. J. Biol. Chem. 273: 35095–35101, 1998.

[27263] Further studies establishing the function and utilities of KCNA2B are found in John Hopkins OMIM database record ID 601142, and in cited publications numbered 1548, 284 and 2848–2849 listed in the bibliography section herein–below, which are also hereby incorporated by reference. Metastasis-associated 1-like 1 (MTA1L1, Accession NM\_004739) is another VGAM659 host target gene. MTA1L1 BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by MTA1L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTA1L1 BINDING SITE, designated SEQ ID:11137, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27264] Another function of VGAM659 is therefore inhibition of Metastasis-associated 1-like 1 (MTA1L1, Accession NM\_004739), a gene which regulates histone deacetylase core complex enzymatic activity. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTA1L1. The function of MTA1L1 has been established by previous studies. The p53 tumor suppressor (OMIM Ref. No. 191170) is a transcriptional factor whose activity is modulated by protein stability and posttranslational modifications including acetylation. Luo et al. (2000) showed that deacetylation of p53 is mediated by a histone deacetylase-1 (HDAC1; 601241)-containing complex. They also purified a p53 target protein, which they named PID, in the deacetylase complexes. PID is identical to MTA1L1,

also called MTA2, which had been identified as a component of the nucleosome remodeling and histone deacetylation (NURD) complex. The authors found that MTA1L1 specifically interacts with p53 both in vitro and in vivo, and its expression reduces significantly the steady-state levels of acetylated p53. MTA1L1 expression strongly represses p53-dependent transcriptional activation, and, notably, it modulates p53-mediated cell growth arrest and apoptosis. Luo et al. (2000) concluded that their results show that deacetylation and functional interactions between the MTA1L1-associated NURD complex may represent an important pathway to regulate p53 function. Zhang et al. (1999) showed that MTA2 and the 32-kD MBD3 (OMIM Ref. No. 603573) protein are subunits of the NURD complex. Immunoprecipitation analysis showed that MBD3 interacts with HDAC1, RBBP4 (OMIM Ref. No. 602923), and RBBP7 (OMIM Ref. No. 602922), but not with MI2 (CHD4; 603277), suggesting that MBD3 is embedded within the NURD complex. The authors found that MTA2 directs the assembly of an active histone deacetylase complex and that the association of MTA2 with the complex requires MBD3. Gel mobility shift analysis determined that both NURD and MBD3 are unable to bind to methy-

lated DNA in the absence of MBD2 (OMIM Ref. No. 603547). Zhang et al. (1999) proposed that NURD is involved in the transcriptional repression of methylated DNA. Wade et al. (1999) also identified MTA1, MTA1L, and MBD3 as components of the NURD complex, which they referred to as the MI2 complex.

[27265] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27266] Futamura, M.; Nishimori, H.; Shiratsuchi, T.; Saji, S.; Nakamura, Y.; Tokino, T. : Molecular cloning, mapping, and characterization of a novel human gene, MTA1-L1, showing homology to a metastasis-associated gene, MTA1. J. Hum. Genet. 44: 52-56, 1999. ; and

[27267] Luo, J.; Su, F.; Chen, D.; Shiloh, A.; Gu, W. : Deacetylation of p53 modulates its effect on cell growth and apoptosis. Nature 408: 377-381, 2000.

[27268] Further studies establishing the function and utilities of MTA1L1 are found in John Hopkins OMIM database record ID 603947, and in cited publications numbered 635, 752 and 5173 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neuroligin 1 (NLGN1, Accession NM\_014932) is an-

other VGAM659 host target gene. NLGN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NLGN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NLGN1 BINDING SITE, designated SEQ ID:17230, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27269] Another function of VGAM659 is therefore inhibition of Neuroligin 1 (NLGN1, Accession NM\_014932), a gene which may trigger the de novo formation of presynaptic structure. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NLGN1. The function of NLGN1 has been established by previous studies. Neurexins (see OMIM Ref. No. NRXN1; 600565) are neuronal cell surface proteins first identified in rat brain with hundreds of isoforms generated by alternative splicing. Ichtchenko et al. (1995) described neuroligin I, a neuronal cell surface protein that is enriched in rat synaptic plasma membranes and acts as a splice site-specific ligand for beta-neurexins. (Each of 3 genes encoding neurexins--NRXN1,

NRXN2, and NRXN3--has 2 independent promoters and generates 2 classes of mRNAs. The longer mRNAs encode alpha-neurexins and the shorter mRNAs beta-neurexins.) Neuroligin I binds to beta-neurexins only if they lack an insert in the alternatively spliced sequence of the G domain, and not if they contain an insert. The extracellular sequence of rat neuroligin I is composed of a catalytically inactive esterase domain homologous to acetylcholinesterase. Ichtchenko et al. (1995) used in situ hybridization to demonstrate that alternative splicing of neurexins at the binding site recognized by neuroligin I is highly regulated. These findings support a model whereby alternative splicing of neurexins creates a family of cell surface receptors that confer interactive specificity on their resident neurons. Using an in vitro system, Scheiffele et al. (2000) demonstrated that mouse neuroligin-1 and -2, postsynaptically localized proteins, can trigger the de novo formation of presynaptic structure. Nonneuronal cells engineered to express neuroligins induced morphologic and functional presynaptic differentiation in contacting axons. This activity could be inhibited by addition of a soluble version of beta-neurexin. Furthermore, addition of soluble beta-neurexin to a coculture of defined pre- and



postsynaptic central nervous system (CNS) neurons inhibited synaptic vesicle clustering in axons contacting target neurons. These results suggested that neuroligins are part of the machinery employed during the formation and remodeling of CNS synapses.

[27270] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27271] Ichtchenko, K.; Hata, Y.; Nguyen, T.; Ullrich, B.; Missler, M.; Moomaw, C.; Sudhof, T. C. : Neuroligin 1: a splice site-specific ligand for beta-neurexins. *Cell* 81: 435-443, 1995. ; and

[27272] Scheiffele, P.; Fan, J.; Cho, J.; Fetter, R.; Serafini, T. : Neuroligin expressed in nonneuronal cells triggers presynaptic development in contacting axons. *Cell* 101: 657-669, 2000.

[27273] Further studies establishing the function and utilities of NLGN1 are found in John Hopkins OMIM database record ID 600568, and in cited publications numbered 8170, 836 and 9531 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. O-linked N-acetylglucosamine (GlcNAc) Transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosam

inyl transferase) (OGT, Accession NM\_003605) is another VGAM659 host target gene. OGT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OGT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OGT BINDING SITE, designated SEQ ID:9660, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27274] Another function of VGAM659 is therefore inhibition of O-linked N-acetylglucosamine (GlcNAc) Transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase) (OGT, Accession NM\_003605), a gene which has a role in the glycosylation of nuclear and cytoplasmic proteins. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OGT. The function of OGT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM464. Transient Receptor Potential Cation Channel, Subfamily M, Member 6 (TRPM6, Accession NM\_017662) is

another VGAM659 host target gene. TRPM6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TRPM6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPM6 BINDING SITE, designated SEQ ID:19203, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27275] Another function of VGAM659 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily M, Member 6 (TRPM6, Accession NM\_017662), a gene which contains a predicted ion channel domain and a protein kinase domain. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPM6. The function of TRPM6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM173. Von Hippel-Lindau Syndrome (VHL, Accession NM\_000551) is another VGAM659 host target gene. VHL BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by VHL, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VHL BINDING SITE, designated SEQ ID:6162, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27276] Another function of VGAM659 is therefore inhibition of Von Hippel–Lindau Syndrome (VHL, Accession NM\_000551), a gene which may control rna stability through the selective degradation of rna-bound proteins. Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VHL. The function of VHL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM197.DKFZp434H2226 (Accession XM\_043863) is another VGAM659 host target gene. DKFZp434H2226 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZp434H2226, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434H2226

BINDING SITE, designated SEQ ID:34034, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27277] Another function of VGAM659 is therefore inhibition of DKFZp434H2226 (Accession XM\_043863). Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434H2226. FLJ20758 (Accession NM\_017952) is another VGAM659 host target gene. FLJ20758 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20758, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20758 BINDING SITE, designated SEQ ID:19654, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27278] Another function of VGAM659 is therefore inhibition of FLJ20758 (Accession NM\_017952). Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20758. KIAA0215 (Accession NM\_014735) is another VGAM659 host target gene. KIAA0215 BINDING SITE is HOST TARGET

binding site found in the 5` untranslated region of mRNA encoded by KIAA0215, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0215 BINDING SITE, designated SEQ ID:16384, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27279] Another function of VGAM659 is therefore inhibition of KIAA0215 (Accession NM\_014735). Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0215. LOC152317 (Accession XM\_098189) is another VGAM659 host target gene. LOC152317 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC152317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152317 BINDING SITE, designated SEQ ID:41465, to the nucleotide sequence of VGAM659 RNA, herein designated VGAM RNA, also designated SEQ ID:3370.

[27280] Another function of VGAM659 is therefore inhibition of

LOC152317 (Accession XM\_098189). Accordingly, utilities of VGAM659 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152317. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 660 (VGAM660) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27281] VGAM660 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM660 was detected is described hereinabove with reference to Figs. 1–8.

[27282] VGAM660 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM660 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27283] VGAM660 gene encodes a VGAM660 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM660 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM660 precursor RNA is designated SEQ ID:646, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:646 is located at position 80746 relative to the genome of Meleagrid Herpesvirus 1.

[27284] VGAM660 precursor RNA folds onto itself, forming VGAM660 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27285] An enzyme complex designated DICER COMPLEX, `dices` the VGAM660 folded precursor RNA into VGAM660 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide se-



quence of VGAM660 RNA is designated SEQ ID:3371, and is provided hereinbelow with reference to the sequence listing part.

[27286] VGAM660 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM660 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM660 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[27287] VGAM660 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM660 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM660 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM660 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM660 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27288] The complementary binding of VGAM660 RNA, herein designated VGAM RNA, to host target binding sites on VGAM660 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM660 host target RNA into VGAM660 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27289] It is appreciated that VGAM660 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM660 host target genes. The mRNA of each one of this plurality of VGAM660 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM660 RNA, herein designated VGAM RNA, and which when bound by VGAM660 RNA causes inhibition of translation of respective one or more VGAM660 host target proteins.

[27290] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM660 gene, herein designated VGAM GENE, on one or more VGAM660 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27291] It is yet further appreciated that a function of VGAM660 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM660 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM660 correlate with, and may be deduced from, the identity of the host target genes which VGAM660 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27292] Nucleotide sequences of the VGAM660 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM660 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM660 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM660 are further described hereinbelow with reference to Table 1.

[27293] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM660 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM660 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27294] As mentioned hereinabove with reference to Fig. 1, a function of VGAM660 gene, herein designated VGAM is inhibition of expression of VGAM660 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM660 correlate with, and may be deduced from, the identity of the target genes which VGAM660 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27295] LOC92106 (Accession NM\_138381) is a VGAM660 host target gene. LOC92106 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92106 BINDING SITE, designated SEQ ID:28755, to the nucleotide sequence of VGAM660 RNA, herein designated VGAM RNA, also designated SEQ ID:3371.

[27296] A function of VGAM660 is therefore inhibition of LOC92106 (Accession NM\_138381). Accordingly, utilities of VGAM660 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92106. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 661 (VGAM661) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27297] VGAM661 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM661 was detected is described hereinabove with reference to Figs. 1–8.

[27298] VGAM661 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Heliothis Zea Virus 1 (HZV–1). VGAM661 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27299] VGAM661 gene encodes a VGAM661 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM661 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM661 precursor RNA is designated SEQ ID:647, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:647 is

located at position 4270 relative to the genome of Heliothis Zea Virus 1 (HZV-1).

[27300] VGAM661 precursor RNA folds onto itself, forming VGAM661 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27301] An enzyme complex designated DICER COMPLEX, `dices` the VGAM661 folded precursor RNA into VGAM661 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 83%) nucleotide sequence of VGAM661 RNA is designated SEQ ID:3372, and is provided hereinbelow with reference to the sequence listing part.

[27302] VGAM661 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM661 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM661 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[27303] VGAM661 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM661 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM661 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM661 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM661 host target RNA,



herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27304] The complementary binding of VGAM661 RNA, herein designated VGAM RNA, to host target binding sites on VGAM661 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM661 host target RNA into VGAM661 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27305] It is appreciated that VGAM661 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM661 host target genes. The mRNA of each one of this plurality of VGAM661 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM661 RNA, herein designated VGAM RNA, and which when bound by VGAM661 RNA causes inhibition of translation of respective one or more VGAM661

host target proteins.

[27306] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM661 gene, herein designated VGAM GENE, on one or more VGAM661 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27307] It is yet further appreciated that a function of VGAM661 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM661 include diagnosis, prevention and treatment of viral infection by Heliothis Zea Virus 1

(HZV-1). Specific functions, and accordingly utilities, of VGAM661 correlate with, and may be deduced from, the identity of the host target genes which VGAM661 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27308] Nucleotide sequences of the VGAM661 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM661 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM661 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM661 are further described hereinbelow with reference to Table 1.

[27309] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM661 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM661 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27310] As mentioned hereinabove with reference to Fig. 1, a function of VGAM661 gene, herein designated VGAM is inhibition of expression of VGAM661 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM661 correlate with, and may be deduced from, the identity of the target genes which VGAM661 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27311] TSG (Accession NM\_020648) is a VGAM661 host target gene. TSG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSG BINDING SITE, designated SEQ ID:21810, to the nucleotide sequence of VGAM661 RNA, herein designated VGAM RNA, also designated SEQ ID:3372.

[27312] A function of VGAM661 is therefore inhibition of TSG (Accession NM\_020648). Accordingly, utilities of VGAM661 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSG. Zinc Finger Protein 214 (ZNF214, Accession NM\_013249) is another VGAM661 host target gene. ZNF214 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZNF214, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of ZNF214 BINDING SITE, designated SEQ ID:14910, to the nucleotide sequence of VGAM661 RNA, herein designated VGAM RNA, also designated SEQ ID:3372.

[27313] Another function of VGAM661 is therefore inhibition of Zinc Finger Protein 214 (ZNF214, Accession NM\_013249). Accordingly, utilities of VGAM661 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF214. ALDH9 (Accession NM\_000696) is another VGAM661 host target gene. ALDH9 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ALDH9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALDH9 BINDING SITE, designated SEQ ID:6359, to the nucleotide sequence of VGAM661 RNA, herein designated VGAM RNA, also designated SEQ ID:3372.

[27314] Another function of VGAM661 is therefore inhibition of ALDH9 (Accession NM\_000696). Accordingly, utilities of VGAM661 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALDH9. LIM and SH3 Protein 1 (LASP1, Accession NM\_006148) is

another VGAM661 host target gene. LASP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LASP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LASP1 BINDING SITE, designated SEQ ID:12790, to the nucleotide sequence of VGAM661 RNA, herein designated VGAM RNA, also designated SEQ ID:3372.

[27315] Another function of VGAM661 is therefore inhibition of LIM and SH3 Protein 1 (LASP1, Accession NM\_006148). Accordingly, utilities of VGAM661 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LASP1. LOC121504 (Accession XM\_058571) is another VGAM661 host target gene. LOC121504 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC121504, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC121504 BINDING SITE, designated SEQ ID:36669, to the nucleotide sequence of VGAM661 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3372.

[27316] Another function of VGAM661 is therefore inhibition of LOC121504 (Accession XM\_058571). Accordingly, utilities of VGAM661 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC121504. LOC153937 (Accession XM\_087813) is another VGAM661 host target gene. LOC153937 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC153937, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153937 BINDING SITE, designated SEQ ID:39444, to the nucleotide sequence of VGAM661 RNA, herein designated VGAM RNA, also designated SEQ ID:3372.

[27317] Another function of VGAM661 is therefore inhibition of LOC153937 (Accession XM\_087813). Accordingly, utilities of VGAM661 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153937. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 662 (VGAM662) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27318] VGAM662 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM662 was detected is described hereinabove with reference to Figs. 1–8.

[27319] VGAM662 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM662 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27320] VGAM662 gene encodes a VGAM662 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM662 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM662 precursor RNA is designated SEQ ID:648, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:648 is located at position 123220 relative to the genome of Vaccinia Virus.

[27321] VGAM662 precursor RNA folds onto itself, forming



VGAM662 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27322] An enzyme complex designated DICER COMPLEX, `dices` the VGAM662 folded precursor RNA into VGAM662 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM662 RNA is designated SEQ ID:3373, and is provided hereinbelow with reference to the sequence listing part.

[27323] VGAM662 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM662 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM662 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[27324] VGAM662 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM662 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM662 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM662 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM662 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27325] The complementary binding of VGAM662 RNA, herein designated VGAM RNA, to host target binding sites on VGAM662 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM662 host target RNA into VGAM662 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27326] It is appreciated that VGAM662 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM662 host target genes. The mRNA of each one of this plurality of VGAM662 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM662 RNA, herein designated VGAM RNA, and which when bound by VGAM662 RNA causes inhibition of translation of respective one or more VGAM662 host target proteins.

[27327] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM662 gene, herein designated VGAM GENE, on one or more VGAM662 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27328] It is yet further appreciated that a function of VGAM662 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM662 correlate with, and may be deduced from, the identity of the host target genes which VGAM662 binds and inhibits, and the

function of these host target genes, as elaborated herein–below.

[27329] Nucleotide sequences of the VGAM662 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM662 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM662 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM662 are further described hereinbelow with reference to Table 1.

[27330] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM662 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM662 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27331] As mentioned hereinabove with reference to Fig. 1, a function of VGAM662 gene, herein designated VGAM is inhibition of expression of VGAM662 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM662 correlate with, and may be deduced from, the identity of the target genes which VGAM662 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[27332] Calcitonin Receptor (CALCR, Accession NM\_001742) is a VGAM662 host target gene. CALCR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CALCR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CALCR BINDING SITE, designated SEQ ID:7479, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27333] A function of VGAM662 is therefore inhibition of Calcitonin Receptor (CALCR, Accession NM\_001742), a gene which is a receptor for calcitonin, is mediated by g proteins which activate adenylyl cyclase, and thought to couple to the heterotrimeric guanosine triphosphate-binding protein that is sensitive to cholera toxin. Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CALCR. The function of CALCR and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM94.Lymphotoxin Alpha (TNF superfam-

ily, member 1) (LTA, Accession NM\_000595) is another VGAM662 host target gene. LTA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LTA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LTA BINDING SITE, designated SEQ ID:6194, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27334] Another function of VGAM662 is therefore inhibition of Lymphotoxin Alpha (TNF superfamily, member 1) (LTA, Accession NM\_000595), a gene which is a cytokine that in its homotrimeric form binds to tnfrsf1a/tnfr1, tnfrsf1b/tnfr and tnfrsf14/hvem. Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LTA. The function of LTA has been established by previous studies. Lymphotoxin was first characterized as a biologic factor in mitogen-stimulated lymphocytes having anticellular activity on neoplastic cell lines. It is a glycoprotein with a relative molecular mass (Mr) of 60,000–70,000, whereas monomeric lymphotoxin has an Mr of 25,000. Gray et al.

(1984) isolated a chemically synthesized gene and natural complementary DNA coding for human lymphotoxin and engineered them for expression in *E. coli*. Cytotoxic and necrosis effects were observed in murine and human tumor cell lines in vitro and in murine sarcomas in vivo.

TNF-beta (also known as lymphotoxin-alpha, or LTA) shows 35% identity and 50% homology in amino acid sequence with the TNF-alpha (OMIM Ref. No. 191160). Aggarwal et al. (1985) showed that the 2 TNFs share a common receptor on tumor cells See 191160 for information on the situation of both TNFA and TNFB on 6p. By analysis of deletions induced in lymphoblastoid cells by gamma-irradiation, Evans et al. (1989) concluded that TNFB maps to the interval between C4 and HLA-B. Spies et al. (1989) showed that the TNF-alpha and TNF-beta gene cluster is about 210 kb from HLA-B on 6p21.3. Jongeneel et al. (1991) described polymorphic microsatellites within a 12-kb region of the major histocompatibility complex that includes the TNFB locus. Lymphotoxin-alpha in a homotrimeric form is a soluble protein secreted by activated lymphocytes and presumed to act as a modulator in the immune response. The LT-alpha homotrimer shares its receptor with tumor necrosis factor and binds to both TNF



receptor-1 (OMIM Ref. No. 191190) and -2 (191191

[27335] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27336] Aggarwal, B. B.; Eessalu, T. E.; Hass, P. E. : Characterization of receptors for human tumour necrosis factor and their regulation by gamma-interferon. Nature 318: 665-667, 1985. ; and

[27337] Evans, A. M.; Petersen, J. W.; Sekhon, G. S.; DeMars, R. : Mapping of prolactin and tumor necrosis factor-beta genes on human chromosome 6p using lymphoblastoid cell deletion mutants. Somat.

[27338] Further studies establishing the function and utilities of LTA are found in John Hopkins OMIM database record ID 153440, and in cited publications numbered 663-66 and 3544 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc-fingers and Homeoboxes 1 (ZHX1, Accession NM\_007222) is another VGAM662 host target gene. ZHX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZHX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of ZHX1 BINDING SITE, designated SEQ ID:14091, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27339] Another function of VGAM662 is therefore inhibition of Zinc-fingers and Homeoboxes 1 (ZHX1, Accession NM\_007222). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZHX1. DKFZP434C1715 (Accession XM\_098421) is another VGAM662 host target gene. DKFZP434C1715 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434C1715, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434C1715 BINDING SITE, designated SEQ ID:41672, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27340] Another function of VGAM662 is therefore inhibition of DKFZP434C1715 (Accession XM\_098421). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with DKFZP434C1715. FLJ23556 (Accession NM\_024880) is another VGAM662 host target gene. FLJ23556 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23556 BINDING SITE, designated SEQ ID:24318, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27341] Another function of VGAM662 is therefore inhibition of FLJ23556 (Accession NM\_024880). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23556. IDN3 (Accession NM\_133433) is another VGAM662 host target gene. IDN3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IDN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IDN3 BINDING SITE, designated SEQ ID:28510, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ

ID:3373.

[27342] Another function of VGAM662 is therefore inhibition of IDN3 (Accession NM\_133433). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IDN3. KIAA1456 (Accession XM\_040100) is another VGAM662 host target gene. KIAA1456 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1456, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1456 BINDING SITE, designated SEQ ID:33262, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27343] Another function of VGAM662 is therefore inhibition of KIAA1456 (Accession XM\_040100). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1456. Neurexophilin 3 (NXPH3, Accession XM\_037847) is another VGAM662 host target gene. NXPH3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

NXPH3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NXPH3 BINDING SITE, designated SEQ ID:32714, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27344] Another function of VGAM662 is therefore inhibition of Neurexophilin 3 (NXPH3, Accession XM\_037847). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NXPH3. PNPASE (Accession XM\_048088) is another VGAM662 host target gene. PNPASE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PNPASE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PNPASE BINDING SITE, designated SEQ ID:35103, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27345] Another function of VGAM662 is therefore inhibition of PNPASE (Accession XM\_048088). Accordingly, utilities of

VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PNPASE. Zinc Finger Protein 33a (KOX 31) (ZNF33A, Accession XM\_166119) is another VGAM662 host target gene. ZNF33A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZNF33A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF33A BINDING SITE, designated SEQ ID:43896, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27346] Another function of VGAM662 is therefore inhibition of Zinc Finger Protein 33a (KOX 31) (ZNF33A, Accession XM\_166119). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF33A. LOC126282 (Accession XM\_059012) is another VGAM662 host target gene. LOC126282 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC126282, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126282 BINDING SITE, designated SEQ ID:36816, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27347] Another function of VGAM662 is therefore inhibition of LOC126282 (Accession XM\_059012). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126282. LOC144583 (Accession XM\_084907) is another VGAM662 host target gene. LOC144583 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144583, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144583 BINDING SITE, designated SEQ ID:37767, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27348] Another function of VGAM662 is therefore inhibition of LOC144583 (Accession XM\_084907). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC144583. LOC145231 (Accession XM\_096740) is another VGAM662 host target gene. LOC145231 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145231, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145231 BINDING SITE, designated SEQ ID:40518, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27349] Another function of VGAM662 is therefore inhibition of LOC145231 (Accession XM\_096740). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145231. LOC147837 (Accession XM\_085915) is another VGAM662 host target gene. LOC147837 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147837, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147837 BINDING SITE, designated SEQ ID:38392, to the nucleotide sequence of VGAM662 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3373.

[27350] Another function of VGAM662 is therefore inhibition of LOC147837 (Accession XM\_085915). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147837. LOC149910 (Accession XM\_086699) is another VGAM662 host target gene. LOC149910 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149910, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149910 BINDING SITE, designated SEQ ID:38827, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27351] Another function of VGAM662 is therefore inhibition of LOC149910 (Accession XM\_086699). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149910. LOC158160 (Accession XM\_054490) is another VGAM662 host target gene. LOC158160 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158160, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158160 BINDING SITE, designated SEQ ID:36168, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27352] Another function of VGAM662 is therefore inhibition of LOC158160 (Accession XM\_054490). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158160. LOC158292 (Accession XM\_098914) is another VGAM662 host target gene. LOC158292 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158292, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158292 BINDING SITE, designated SEQ ID:41932, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27353] Another function of VGAM662 is therefore inhibition of LOC158292 (Accession XM\_098914). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC158292. LOC162333 (Accession XM\_102591) is another VGAM662 host target gene. LOC162333 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC162333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162333 BINDING SITE, designated SEQ ID:42129, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27354] Another function of VGAM662 is therefore inhibition of LOC162333 (Accession XM\_102591). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162333. LOC202018 (Accession XM\_114420) is another VGAM662 host target gene. LOC202018 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202018, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202018 BINDING SITE, designated SEQ ID:42958, to

the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27355] Another function of VGAM662 is therefore inhibition of LOC202018 (Accession XM\_114420). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202018. LOC219392 (Accession XM\_165921) is another VGAM662 host target gene. LOC219392 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219392, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219392 BINDING SITE, designated SEQ ID:43799, to the nucleotide sequence of VGAM662 RNA, herein designated VGAM RNA, also designated SEQ ID:3373.

[27356] Another function of VGAM662 is therefore inhibition of LOC219392 (Accession XM\_165921). Accordingly, utilities of VGAM662 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219392. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 663 (VGAM663) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27357] VGAM663 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM663 was detected is described hereinabove with reference to Figs. 1–8.

[27358] VGAM663 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rachiplusia Ou Multiple Nucleopolyhedrovirus. VGAM663 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27359] VGAM663 gene encodes a VGAM663 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM663 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM663 precursor RNA is designated SEQ ID:649, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:649 is located at position 325 relative to the genome of Rachiplusia Ou Multiple Nucleopolyhedrovirus.

[27360] VGAM663 precursor RNA folds onto itself, forming VGAM663 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27361] An enzyme complex designated DICER COMPLEX, `dices` the VGAM663 folded precursor RNA into VGAM663 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM663 RNA is designated SEQ ID:3374, and is provided hereinbelow with reference to the sequence listing part.

[27362] VGAM663 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM663 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM663 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27363] VGAM663 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM663 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM663 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM663 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM663 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27364] The complementary binding of VGAM663 RNA, herein designated VGAM RNA, to host target binding sites on VGAM663 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM663 host target RNA into VGAM663 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27365] It is appreciated that VGAM663 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM663 host target genes. The mRNA of each one of this plurality of VGAM663 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM663 RNA, herein designated VGAM RNA, and which when bound by VGAM663 RNA causes inhibition of translation of respective one or more VGAM663 host target proteins.

[27366] It is further appreciated by one skilled in the art that the



mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM663 gene, herein designated VGAM GENE, on one or more VGAM663 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27367] It is yet further appreciated that a function of VGAM663 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of viral infection by Rachiplusia Ou Multiple Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM663 correlate with, and may be deduced

from, the identity of the host target genes which VGAM663 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27368] Nucleotide sequences of the VGAM663 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM663 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM663 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM663 are further described hereinbelow with reference to Table 1.

[27369] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM663 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM663 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27370] As mentioned hereinabove with reference to Fig. 1, a function of VGAM663 gene, herein designated VGAM is inhibition of expression of VGAM663 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM663 correlate with, and may be deduced from, the identity of the target genes which VGAM663

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27371] B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993) is a VGAM663 host target gene. BCL7A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL7A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL7A BINDING SITE, designated SEQ ID:21985, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27372] A function of VGAM663 is therefore inhibition of B-cell CLL/lymphoma 7A (BCL7A, Accession NM\_020993). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL7A. Chloride Channel 4 (CLCN4, Accession NM\_001830) is another VGAM663 host target gene. CLCN4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CLCN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of CLCN4 BINDING SITE, designated SEQ ID:7573, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27373] Another function of VGAM663 is therefore inhibition of Chloride Channel 4 (CLCN4, Accession NM\_001830), a gene which is regulation of cell volume; membrane potential stabilization, signal transduction and transepithelial transport. Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCN4. The function of CLCN4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM558. Zinc Finger Protein 264 (ZNF264, Accession NM\_003417) is another VGAM663 host target gene. ZNF264 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF264, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF264 BINDING SITE, designated SEQ ID:9458, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM

RNA, also designated SEQ ID:3374.

[27374] Another function of VGAM663 is therefore inhibition of Zinc Finger Protein 264 (ZNF264, Accession NM\_003417). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF264. DKFZP761F241 (Accession NM\_031455) is another VGAM663 host target gene. DKFZP761F241 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP761F241, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP761F241 BINDING SITE, designated SEQ ID:25474, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27375] Another function of VGAM663 is therefore inhibition of DKFZP761F241 (Accession NM\_031455). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP761F241. FLJ10008 (Accession NM\_017970) is another VGAM663 host target gene. FLJ10008 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by FLJ10008, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10008 BINDING SITE, designated SEQ ID:19690, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27376] Another function of VGAM663 is therefore inhibition of FLJ10008 (Accession NM\_017970). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10008. TSPAN-2 (Accession NM\_005725) is another VGAM663 host target gene. TSPAN-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSPAN-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSPAN-2 BINDING SITE, designated SEQ ID:12279, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27377] Another function of VGAM663 is therefore inhibition of TSPAN-2 (Accession NM\_005725). Accordingly, utilities of

VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSPAN-2. Zinc Finger, DHHC Domain Containing 3 (ZDHHC3, Accession NM\_016598) is another VGAM663 host target gene. ZDHHC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZDHHC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZDHHC3 BINDING SITE, designated SEQ ID:18685, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27378] Another function of VGAM663 is therefore inhibition of Zinc Finger, DHHC Domain Containing 3 (ZDHHC3, Accession NM\_016598). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZDHHC3. LOC205095 (Accession XM\_119820) is another VGAM663 host target gene. LOC205095 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC205095, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC205095 BINDING SITE, designated SEQ ID:43600, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27379] Another function of VGAM663 is therefore inhibition of LOC205095 (Accession XM\_119820). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC205095. LOC221272 (Accession XM\_168050) is another VGAM663 host target gene. LOC221272 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221272, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221272 BINDING SITE, designated SEQ ID:44963, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27380] Another function of VGAM663 is therefore inhibition of LOC221272 (Accession XM\_168050). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC221272. LOC92078 (Accession XM\_042684) is another VGAM663 host target gene. LOC92078 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92078 BINDING SITE, designated SEQ ID:33739, to the nucleotide sequence of VGAM663 RNA, herein designated VGAM RNA, also designated SEQ ID:3374.

[27381] Another function of VGAM663 is therefore inhibition of LOC92078 (Accession XM\_042684). Accordingly, utilities of VGAM663 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92078. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 664 (VGAM664) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27382] VGAM664 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM664 was detected is described hereinabove with reference to Figs. 1–8.

[27383] VGAM664 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rachiplusia Ou Multiple Nucleopolyhedrovirus. VGAM664 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27384] VGAM664 gene encodes a VGAM664 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM664 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM664 precursor RNA is designated SEQ ID:650, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:650 is located at position 18 relative to the genome of Rachiplusia Ou Multiple Nucleopolyhedrovirus.

[27385] VGAM664 precursor RNA folds onto itself, forming VGAM664 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27386] An enzyme complex designated DICER COMPLEX, `dices` the VGAM664 folded precursor RNA into VGAM664 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM664 RNA is designated SEQ ID:3375, and is provided hereinbelow with reference to the sequence listing part.

[27387] VGAM664 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM664 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM664 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27388] VGAM664 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM664 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM664 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM664 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM664 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27389] The complementary binding of VGAM664 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM664 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM664 host target RNA into VGAM664 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27390] It is appreciated that VGAM664 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM664 host target genes. The mRNA of each one of this plurality of VGAM664 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM664 RNA, herein designated VGAM RNA, and which when bound by VGAM664 RNA causes inhibition of translation of respective one or more VGAM664 host target proteins.

[27391] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM664 gene, herein designated VGAM GENE, on one or more VGAM664 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27392] It is yet further appreciated that a function of VGAM664 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM664 include diagnosis, prevention and treatment of viral infection by Rachiplusia Ou Multiple Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM664 correlate with, and may be deduced from, the identity of the host target genes which VGAM664 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27393] Nucleotide sequences of the VGAM664 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM664 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM664 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM664 are further described hereinbelow with reference to Table 1.

[27394] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM664 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM664 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27395] As mentioned hereinabove with reference to Fig. 1, a function of VGAM664 gene, herein designated VGAM is inhibition of expression of VGAM664 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM664 correlate with, and may be deduced from, the identity of the target genes which VGAM664 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27396] BCMP1 (Accession NM\_031442) is a VGAM664 host target gene. BCMP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCMP1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCMP1 BINDING SITE, designated SEQ ID:25458, to the nucleotide sequence of VGAM664 RNA, herein designated VGAM RNA, also designated SEQ ID:3375.

[27397] A function of VGAM664 is therefore inhibition of BCMP1 (Accession NM\_031442). Accordingly, utilities of VGAM664 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCMP1. FLJ20294 (Accession NM\_017749) is another VGAM664 host target gene. FLJ20294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20294 BINDING SITE, designated SEQ ID:19350, to the nucleotide sequence of VGAM664 RNA, herein designated VGAM RNA, also designated SEQ ID:3375.

[27398] Another function of VGAM664 is therefore inhibition of FLJ20294 (Accession NM\_017749). Accordingly, utilities of VGAM664 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with FLJ20294. KIAA0446 (Accession XM\_044155) is another VGAM664 host target gene. KIAA0446 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0446 BINDING SITE, designated SEQ ID:34145, to the nucleotide sequence of VGAM664 RNA, herein designated VGAM RNA, also designated SEQ ID:3375.

[27399] Another function of VGAM664 is therefore inhibition of KIAA0446 (Accession XM\_044155). Accordingly, utilities of VGAM664 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0446. START Domain Containing 7 (STARD7, Accession NM\_139267) is another VGAM664 host target gene. STARD7 BINDING SITE1 and STARD7 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by STARD7, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STARD7 BINDING

SITE1 and STARD7 BINDING SITE2, designated SEQ ID:29258 and SEQ ID:21354 respectively, to the nucleotide sequence of VGAM664 RNA, herein designated VGAM RNA, also designated SEQ ID:3375.

[27400] Another function of VGAM664 is therefore inhibition of START Domain Containing 7 (STARD7, Accession NM\_139267). Accordingly, utilities of VGAM664 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STARD7. LOC122786 (Accession XM\_058660) is another VGAM664 host target gene. LOC122786 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC122786, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC122786 BINDING SITE, designated SEQ ID:36698, to the nucleotide sequence of VGAM664 RNA, herein designated VGAM RNA, also designated SEQ ID:3375.

[27401] Another function of VGAM664 is therefore inhibition of LOC122786 (Accession XM\_058660). Accordingly, utilities of VGAM664 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC122786. LOC158696 (Accession XM\_088644) is another VGAM664 host target gene. LOC158696 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158696 BINDING SITE, designated SEQ ID:39881, to the nucleotide sequence of VGAM664 RNA, herein designated VGAM RNA, also designated SEQ ID:3375.

[27402] Another function of VGAM664 is therefore inhibition of LOC158696 (Accession XM\_088644). Accordingly, utilities of VGAM664 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158696. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 665 (VGAM665) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27403] VGAM665 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM665 was detected is described hereinabove with reference to Figs. 1–8.

[27404] VGAM665 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rachiplusia Ou Multiple Nucleopolyhedrovirus. VGAM665 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27405] VGAM665 gene encodes a VGAM665 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM665 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM665 precursor RNA is designated SEQ ID:651, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:651 is located at position 235 relative to the genome of Rachiplusia Ou Multiple Nucleopolyhedrovirus.

[27406] VGAM665 precursor RNA folds onto itself, forming VGAM665 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27407] An enzyme complex designated DICER COMPLEX, `dices` the VGAM665 folded precursor RNA into VGAM665 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM665 RNA is designated SEQ ID:3376, and is provided hereinbelow with reference to the sequence listing part.

[27408] VGAM665 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM665 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM665 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27409] VGAM665 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM665 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM665 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM665 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM665 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27410] The complementary binding of VGAM665 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM665 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM665 host target RNA into VGAM665 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27411] It is appreciated that VGAM665 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM665 host target genes. The mRNA of each one of this plurality of VGAM665 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM665 RNA, herein designated VGAM RNA, and which when bound by VGAM665 RNA causes inhibition of translation of respective one or more VGAM665 host target proteins.

[27412] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM665 gene, herein designated VGAM GENE, on one or more VGAM665 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27413] It is yet further appreciated that a function of VGAM665 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of viral infection by Rachiplusia Ou Multiple Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM665 correlate with, and may be deduced from, the identity of the host target genes which VGAM665 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27414] Nucleotide sequences of the VGAM665 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM665 RNA, herein designated VGAM RNA,



and a schematic representation of the secondary folding of VGAM665 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM665 are further described hereinbelow with reference to Table 1.

[27415] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM665 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM665 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27416] As mentioned hereinabove with reference to Fig. 1, a function of VGAM665 gene, herein designated VGAM is inhibition of expression of VGAM665 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM665 correlate with, and may be deduced from, the identity of the target genes which VGAM665 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27417] ATPase, Class VI, Type 11B (ATP11B, Accession XM\_087254) is a VGAM665 host target gene. ATP11B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP11B, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP11B BINDING SITE, designated SEQ ID:39144, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27418] A function of VGAM665 is therefore inhibition of ATPase, Class VI, Type 11B (ATP11B, Accession XM\_087254), a gene which is phosphorylated in their intermediate state, drives uphill transport of ions across membranes. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP11B. The function of ATP11B has been established by previous studies. Nagase et al. (1999) isolated a partial cDNA encoding ATP11B, which they called KIAA0956, from a brain cDNA library. Based on homology analysis, they predicted that the KIAA0956 protein is a chromaffin granule ATPase. RT-PCR analysis detected wide expression, with highest levels in kidney, followed by ovary, corpus callosum, and testis. RUSH proteins are SWI/SNF-related transcription factors with uteroglobin promoter-binding RING finger signatures near their C termini (see OMIM Ref. No. 603257). Mansharamani et al. (2001)

isolated a nearly full-length rabbit cDNA encoding Rfbp, a RUSH-binding protein that shares 93% amino acid identity with KIAA0956.

[27419] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27420] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Hiro-sawa, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. XIII. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. DNA Res. 6: 63-70, 1999. ; and

[27421] Mansharamani, M.; Hewetson, A.; Chilton, B. S. : Cloning and characterization of an atypical type IV P-type ATPase that binds to the RING motif of RUSH transcription factors. J. Biol. C.

[27422] Further studies establishing the function and utilities of ATP11B are found in John Hopkins OMIM database record ID 605869, and in cited publications numbered 6623, 700 and 8593 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633) is another VGAM665 host target gene. BCL2 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2 BINDING SITE, designated SEQ ID:6260, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27423] Another function of VGAM665 is therefore inhibition of B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633). Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL2. F-box and Leucine-rich Repeat Protein 5 (FBXL5, Accession NM\_012161) is another VGAM665 host target gene. FBXL5 BINDING SITE1 and FBXL5 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FBXL5, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXL5 BINDING SITE1 and FBXL5 BINDING SITE2, designated SEQ ID:14461 and SEQ ID:27303 respectively, to the nucleotide sequence of VGAM665 RNA,

herein designated VGAM RNA, also designated SEQ ID:3376.

[27424] Another function of VGAM665 is therefore inhibition of F-box and Leucine-rich Repeat Protein 5 (FBXL5, Accession NM\_012161), a gene which is a putative SCF ubiquitin ligase subunit involved in protein degradation. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXL5. The function of FBXL5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM61. Fibroblast Growth Factor 5 (FGF5, Accession NM\_033143) is another VGAM665 host target gene. FGF5 BINDING SITE1 and FGF5 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGF5, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF5 BINDING SITE1 and FGF5 BINDING SITE2, designated SEQ ID:27003 and SEQ ID:7782 respectively, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27425] Another function of VGAM665 is therefore inhibition of Fibroblast Growth Factor 5 (FGF5, Accession NM\_033143), a gene which induces transformation and may regulate neuronal differentiation. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF5. The function of FGF5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM276. Interleukin 1 Receptor Antagonist (IL1RN, Accession NM\_000577) is another VGAM665 host target gene. IL1RN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL1RN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL1RN BINDING SITE, designated SEQ ID:6177, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27426] Another function of VGAM665 is therefore inhibition of Interleukin 1 Receptor Antagonist (IL1RN, Accession NM\_000577), a gene which inhibits the activity of il-1 by binding to its receptor. il-1ra has no il-1 like activity. Ac-

cordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL1RN. The function of IL1RN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM193. Protein Phosphatase 1, Catalytic Subunit, Beta Isoform (PPP1CB, Accession NM\_002709) is another VGAM665 host target gene. PPP1CB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1CB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1CB BINDING SITE, designated SEQ ID:8560, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27427] Another function of VGAM665 is therefore inhibition of Protein Phosphatase 1, Catalytic Subunit, Beta Isoform (PPP1CB, Accession NM\_002709), a gene which is the catalytic subunit of protein phosphatase 1. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

PPP1CB. The function of PPP1CB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM46. Selectin E (endothelial adhesion molecule 1) (SELE, Accession NM\_000450) is another VGAM665 host target gene. SELE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SELE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SELE BINDING SITE, designated SEQ ID:6052, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27428] Another function of VGAM665 is therefore inhibition of Selectin E (endothelial adhesion molecule 1) (SELE, Accession NM\_000450), a gene which expressed on cytokine induced endothelial cells and mediates their binding to leukocytes. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SELE. The function of SELE and its association with various diseases and clinical conditions, has been established by previous studies, as de-



scribed hereinabove with reference to VGAM508. Single-minded Homolog 1 (Drosophila) (SIM1, Accession NM\_005068) is another VGAM665 host target gene. SIM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIM1 BINDING SITE, designated SEQ ID:11512, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27429] Another function of VGAM665 is therefore inhibition of Single-minded Homolog 1 (Drosophila) (SIM1, Accession NM\_005068), a gene which may have pleiotropic effects during embryogenesis and in the adult. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIM1. The function of SIM1 has been established by previous studies. Studies of mice and humans have revealed a number of genes that when mutated result in severe obesity. Holder et al. (2000) studied a girl with early-onset obesity and a balanced translocation between 1p22.1 and 6q16.2. At 67 months of age she weighed 47.5 kg (+9.3

SD) and was 127.2 cm tall (+3.2 SD); her weight for height was +6.3 SD. The child displayed an aggressive, voracious appetite, and the obesity was thought to be due to high intake, since measured energy expenditure was normal. Holder et al. (2000) cloned and sequenced both translocation breakpoints. The translocation did not appear to affect any transcription unit on 1p, but it disrupted the SIM1 gene on 6q, separating the 5-prime promoter region and the bHLH domain from the 3-prime PAS and putative transcriptional regulation domains. The transcriptional targets of SIM1 were not known. Mouse Sim1 is expressed in the developing kidney and central nervous system and is essential for formation of the supraoptic and paraventricular (PVN) nuclei of the hypothalamus. Previous neuroanatomic and pharmacologic studies had implicated the PVN in the regulation of body weight: PVN neurons express the melanocortin-4 receptor (MC4R; 155541) and appear to be physiologic targets of alpha-melanocyte-stimulating hormone (OMIM Ref. No. 176830), which inhibits food intake. Holder et al. (2000) hypothesized that haploinsufficiency of SIM1, possibly acting upstream or downstream of MC4R in the PVN, was responsible for severe obesity in their patient. Animal

model experiments lend further support to the function of SIM1. Mice homozygous for a null allele of Sim1 (Sim1 – /–) lack a paraventricular nucleus (PVN) and die perinatally. In contrast, Michaud et al. (2001) showed that Sim1 heterozygous mice were viable but developed early-onset obesity, with increased linear growth, hyperinsulinemia, and hyperleptinemia. Sim1 +/- mice were hyperphagic but their energy expenditure was not decreased, distinguishing them from other mouse models of early-onset obesity such as deficiencies in leptin (OMIM Ref. No. 164160) and melanocortin receptor-4 (OMIM Ref. No. 155541). Quantitative histologic comparison with normal littermates showed that the PVN of Sim1 +/- mice contains on average 24% fewer cells without a selective loss of any identifiable major cell type. Since acquired lesions in the PVN also induce increased appetite without a decrease in energy expenditure, the authors proposed that abnormalities of PVN development may cause the obesity of Sim1 +/- mice.

[27430] It is appreciated that the abovementioned animal model for SIM1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[27431] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27432] Holder, J. L., Jr.; Butte, N. F.; Zinn, A. R. : Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. Hum. Molec. Genet. 9: 101–108, 2000. ; and

[27433] Michaud, J. L.; Boucher, F.; Melnyk, A.; Gauthier, F.; Goshu, E.; Levy, E.; Mitchell, G. A.; Himms–Hagen, J.; Fan, C.–M. : Sim1 haploinsufficiency causes hyperphagia, obesity and redu.

[27434] Further studies establishing the function and utilities of SIM1 are found in John Hopkins OMIM database record ID 603128, and in cited publications numbered 64 and 647–646 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Visual System Homeobox 1 Homolog, CHX10–like (zebrafish) (VSX1, Accession NM\_014588) is another VGAM665 host target gene. VSX1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by VSX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VSX1 BINDING SITE, designated SEQ

ID:15955, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27435] Another function of VGAM665 is therefore inhibition of Visual System Homeobox 1 Homolog, CHX10-like (zebrafish) (VSX1, Accession NM\_014588), a gene which is implicated in ocular development. Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VSX1. The function of VSX1 has been established by previous studies. Using a yeast 1-hybrid screen of an adult bovine retinal cDNA library with the conserved core of the red/green visual pigment locus control region (see OMIM Ref. No. CBD; 303800) as bait, followed by RT-PCR of a human retinal library, Hayashi et al. (2000) isolated a cDNA encoding VSX1, which they termed RINX for 'retinal inner nuclear layer (INL) homeo box.' Hayashi et al. (2000) also identified 5 splice variants of VSX1. RT-PCR analysis indicated that the 2 major VSX1 transcripts are expressed in retina and WERI, a retinoblastoma cell line expressing retinal cone genes, but not in other tissues or in a rhodopsin-expressing retinoblastoma cell line. Northern blot analysis detected a 2.0-kb main VSX1 transcript in

retina but not heart. In situ hybridization analysis of bovine retinal sections demonstrated exclusive localization of VSX1 to cell nuclei in the middle of the INL, likely belonging to bipolar cells. By PCR of a human embryonic craniofacial cDNA library using degenerate oligonucleotides based on highly conserved motifs within the paired-like homeodomain, Semina et al. (2000) isolated a cDNA encoding VSX1. The predicted 365-amino acid VSX1 protein contains a paired-like homeodomain and a CVC domain. Human VSX1 shares 55% overall sequence identity with the zebrafish and goldfish Vsx1 proteins and 35% overall identity with the goldfish Vsx2 and mouse Chx10 proteins. PCR of a panel of cDNA libraries detected VSX1 expression in embryonic craniofacial, adult retina, and adult cornea libraries but not in adult lens, embryonic or adult brain, heart, kidney, liver, lung, skeletal muscle, spleen, or thymus libraries.

[27436] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27437] Hayashi, T.; Huang, J.; Deeb, S. S. : RINX(VSX1), a novel homeobox gene expressed in the inner nuclear layer of the adult retina. *Genomics* 67: 128–139, 2000. ; and

[27438] Semina, E. V.; Mintz-Hittner, H. A.; Murray, J. C. : Isolation and characterization of a novel human paired-like home-domain-containing transcription factor gene, VSX1, expressed in ocula.

[27439] Further studies establishing the function and utilities of VSX1 are found in John Hopkins OMIM database record ID 605020, and in cited publications numbered 4387-4389 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger Protein 264 (ZNF264, Accession NM\_003417) is another VGAM665 host target gene. ZNF264 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF264, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF264 BINDING SITE, designated SEQ ID:9459, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27440] Another function of VGAM665 is therefore inhibition of Zinc Finger Protein 264 (ZNF264, Accession NM\_003417). Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with ZNF264. DKFZP564O0463 (Accession NM\_014156) is another VGAM665 host target gene. DKFZP564O0463 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564O0463, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564O0463 BINDING SITE, designated SEQ ID:15441, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27441] Another function of VGAM665 is therefore inhibition of DKFZP564O0463 (Accession NM\_014156). Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564O0463. KIAA0226 (Accession XM\_032901) is another VGAM665 host target gene. KIAA0226 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0226, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0226 BINDING SITE, designated SEQ ID:31787, to the



nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27442] Another function of VGAM665 is therefore inhibition of KIAA0226 (Accession XM\_032901). Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0226. KIAA0534 (Accession XM\_049349) is another VGAM665 host target gene. KIAA0534 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0534, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0534 BINDING SITE, designated SEQ ID:35377, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27443] Another function of VGAM665 is therefore inhibition of KIAA0534 (Accession XM\_049349). Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0534. KIAA1193 (Accession XM\_041843) is another VGAM665 host target gene. KIAA1193 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1193, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1193 BINDING SITE, designated SEQ ID:33579, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27444] Another function of VGAM665 is therefore inhibition of KIAA1193 (Accession XM\_041843). Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1193. KIAA1622 (Accession NM\_058237) is another VGAM665 host target gene. KIAA1622 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1622, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1622 BINDING SITE, designated SEQ ID:27765, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27445] Another function of VGAM665 is therefore inhibition of KIAA1622 (Accession NM\_058237). Accordingly, utilities

of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1622. LOC116064 (Accession XM\_057296) is another VGAM665 host target gene. LOC116064 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC116064, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC116064 BINDING SITE, designated SEQ ID:36496, to the nucleotide sequence of VGAM665 RNA, herein designated VGAM RNA, also designated SEQ ID:3376.

[27446] Another function of VGAM665 is therefore inhibition of LOC116064 (Accession XM\_057296). Accordingly, utilities of VGAM665 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116064. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 666 (VGAM666) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27447] VGAM666 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM666 was detected is described hereinabove with reference to Figs. 1–8.

[27448] VGAM666 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Yaba-like Disease Virus. VGAM666 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27449] VGAM666 gene encodes a VGAM666 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM666 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM666 precursor RNA is designated SEQ ID:652, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:652 is located at position 27927 relative to the genome of Yaba-like Disease Virus.

[27450] VGAM666 precursor RNA folds onto itself, forming VGAM666 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

‘hairpin structure’, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[27451] An enzyme complex designated DICER COMPLEX, ‘dices’ the VGAM666 folded precursor RNA into VGAM666 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, ‘dicing’ of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 78%) nucleotide sequence of VGAM666 RNA is designated SEQ ID:3377, and is provided hereinbelow with reference to the sequence listing part.

[27452] VGAM666 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM666 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM666 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5’ untranslated region, a protein coding region and a 3’ untranslated region, designated 5’UTR, PROTEIN

CODING and 3`UTR respectively.

[27453] VGAM666 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM666 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM666 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM666 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM666 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27454] The complementary binding of VGAM666 RNA, herein designated VGAM RNA, to host target binding sites on VGAM666 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM666 host target RNA into VGAM666 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27455] It is appreciated that VGAM666 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM666 host target genes. The mRNA of each one of this plurality of VGAM666 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM666 RNA, herein designated VGAM RNA, and which when bound by VGAM666 RNA causes inhibition of translation of respective one or more VGAM666 host target proteins.

[27456] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM666 gene, herein designated VGAM GENE, on one or more VGAM666 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27457] It is yet further appreciated that a function of VGAM666 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM666 include diagnosis, prevention and treatment of viral infection by Yaba-like Disease Virus. Specific functions, and accordingly utilities, of VGAM666 correlate with, and may be deduced from, the identity of the host target genes which VGAM666 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27458] Nucleotide sequences of the VGAM666 precursor RNA,



herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM666 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM666 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM666 are further  
described hereinbelow with reference to Table 1.

[27459] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM666 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM666 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[27460] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM666 gene, herein designated VGAM is  
inhibition of expression of VGAM666 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM666 correlate with, and may be deduced  
from, the identity of the target genes which VGAM666  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[27461] A Kinase (PRKA) Anchor Protein 13 (AKAP13, Accession  
XM\_116974) is a VGAM666 host target gene. AKAP13

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKAP13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP13 BINDING SITE, designated SEQ ID:43175, to the nucleotide sequence of VGAM666 RNA, herein designated VGAM RNA, also designated SEQ ID:3377.

[27462] A function of VGAM666 is therefore inhibition of A Kinase (PRKA) Anchor Protein 13 (AKAP13, Accession XM\_116974), a gene which regulates subcellular localization of type II cAMP-dependent PKA. Accordingly, utilities of VGAM666 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP13. The function of AKAP13 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM17. Ret Proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease) (RET, Accession NM\_020630) is another VGAM666 host target gene. RET BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RET, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RET BINDING SITE, designated SEQ ID:21781, to the nucleotide sequence of VGAM666 RNA, herein designated VGAM RNA, also designated SEQ ID:3377.

[27463] Another function of VGAM666 is therefore inhibition of Ret Proto-oncogene (multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease) (RET, Accession NM\_020630), a gene which transduces signals for cell growth and differentiation. Accordingly, utilities of VGAM666 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RET. The function of RET and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM381. Zinc Finger, DHHC Domain Containing 2 (ZDHHC2, Accession NM\_016353) is another VGAM666 host target gene. ZDHHC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZDHHC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of ZDHHC2 BINDING SITE, designated SEQ ID:18485, to the nucleotide sequence of VGAM666 RNA, herein designated VGAM RNA, also designated SEQ ID:3377.

[27464] Another function of VGAM666 is therefore inhibition of Zinc Finger, DHHC Domain Containing 2 (ZDHHC2, Accession NM\_016353). Accordingly, utilities of VGAM666 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZDHHC2. LOC158263 (Accession XM\_088530) is another VGAM666 host target gene. LOC158263 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158263, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158263 BINDING SITE, designated SEQ ID:39796, to the nucleotide sequence of VGAM666 RNA, herein designated VGAM RNA, also designated SEQ ID:3377.

[27465] Another function of VGAM666 is therefore inhibition of LOC158263 (Accession XM\_088530). Accordingly, utilities of VGAM666 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC158263. LOC221656 (Accession XM\_166418) is another VGAM666 host target gene. LOC221656 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221656, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221656 BINDING SITE, designated SEQ ID:44291, to the nucleotide sequence of VGAM666 RNA, herein designated VGAM RNA, also designated SEQ ID:3377.

[27466] Another function of VGAM666 is therefore inhibition of LOC221656 (Accession XM\_166418). Accordingly, utilities of VGAM666 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221656. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 667 (VGAM667) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27467] VGAM667 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM667 was detected is described hereinabove with reference to Figs. 1–8.

[27468] VGAM667 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM667 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27469] VGAM667 gene encodes a VGAM667 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM667 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM667 precursor RNA is designated SEQ ID:653, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:653 is located at position 242236 relative to the genome of Fowlpox Virus.

[27470] VGAM667 precursor RNA folds onto itself, forming VGAM667 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27471] An enzyme complex designated DICER COMPLEX, `dices` the VGAM667 folded precursor RNA into VGAM667 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM667 RNA is designated SEQ ID:3378, and is provided hereinbelow with reference to the sequence listing part.

[27472] VGAM667 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM667 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM667 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27473] VGAM667 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM667 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM667 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM667 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM667 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27474] The complementary binding of VGAM667 RNA, herein designated VGAM RNA, to host target binding sites on



VGAM667 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM667 host target RNA into VGAM667 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27475] It is appreciated that VGAM667 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM667 host target genes. The mRNA of each one of this plurality of VGAM667 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM667 RNA, herein designated VGAM RNA, and which when bound by VGAM667 RNA causes inhibition of translation of respective one or more VGAM667 host target proteins.

[27476] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM667 gene, herein designated VGAM GENE, on one or more VGAM667 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27477] It is yet further appreciated that a function of VGAM667 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM667 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM667 correlate with, and may be deduced from, the identity of the host target genes which VGAM667 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27478] Nucleotide sequences of the VGAM667 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM667 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM667 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM667 are further described hereinbelow with reference to Table 1.

[27479] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM667 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM667 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27480] As mentioned hereinabove with reference to Fig. 1, a function of VGAM667 gene, herein designated VGAM is inhibition of expression of VGAM667 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM667 correlate with, and may be deduced from, the identity of the target genes which VGAM667 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27481] Glucose-6-phosphatase, Catalytic (glycogen storage disease type I, von Gierke disease) (G6PC, Accession NM\_000151) is a VGAM667 host target gene. G6PC BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by G6PC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of G6PC BINDING SITE, designated SEQ ID:5653, to the nucleotide sequence of VGAM667 RNA, herein designated VGAM RNA, also designated SEQ ID:3378.

[27482] A function of VGAM667 is therefore inhibition of Glucose-6-phosphatase, Catalytic (glycogen storage disease type I, von Gierke disease) (G6PC, Accession NM\_000151). Accordingly, utilities of VGAM667 include diagnosis, prevention and treatment of diseases and clinical conditions associated with G6PC. Solute Carrier Family 16 (monocarboxylic acid transporters), Member 2 (putative transporter) (SLC16A2, Accession NM\_006517) is another VGAM667 host target gene. SLC16A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC16A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC16A2 BINDING SITE, designated SEQ ID:13266, to the nucleotide sequence of VGAM667 RNA, herein designated VGAM

RNA, also designated SEQ ID:3378.

[27483] Another function of VGAM667 is therefore inhibition of Solute Carrier Family 16 (monocarboxylic acid transporters), Member 2 (putative transporter) (SLC16A2, Accession NM\_006517). Accordingly, utilities of VGAM667 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC16A2.

LOC140139 (Accession XM\_067102) is another VGAM667 host target gene. LOC140139 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC140139, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC140139 BINDING SITE, designated SEQ ID:37347, to the nucleotide sequence of VGAM667 RNA, herein designated VGAM RNA, also designated SEQ ID:3378.

[27484] Another function of VGAM667 is therefore inhibition of LOC140139 (Accession XM\_067102). Accordingly, utilities of VGAM667 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC140139. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 668 (VGAM668) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27485] VGAM668 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM668 was detected is described hereinabove with reference to Figs. 1–8.

[27486] VGAM668 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM668 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27487] VGAM668 gene encodes a VGAM668 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM668 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM668 precursor RNA is designated SEQ ID:654, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:654 is located at position 267154 relative to the genome of

## Fowlpox Virus.

[27488] VGAM668 precursor RNA folds onto itself, forming VGAM668 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27489] An enzyme complex designated DICER COMPLEX, `dices` the VGAM668 folded precursor RNA into VGAM668 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM668 RNA is designated SEQ ID:3379, and is provided hereinbelow with reference to the sequence listing part.

[27490] VGAM668 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM668 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM668 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27491] VGAM668 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM668 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM668 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM668 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM668 host target RNA, herein designated VGAM HOST TARGET RNA. It is further



appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27492] The complementary binding of VGAM668 RNA, herein designated VGAM RNA, to host target binding sites on VGAM668 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM668 host target RNA into VGAM668 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27493] It is appreciated that VGAM668 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM668 host target genes. The mRNA of each one of this plurality of VGAM668 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM668 RNA, herein designated VGAM RNA, and which when bound by VGAM668 RNA causes inhibition of translation of respective one or more VGAM668 host target proteins.

[27494] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM668 gene, herein designated VGAM GENE, on one or more VGAM668 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27495] It is yet further appreciated that a function of VGAM668 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM668 correlate

with, and may be deduced from, the identity of the host target genes which VGAM668 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27496] Nucleotide sequences of the VGAM668 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM668 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM668 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM668 are further described hereinbelow with reference to Table 1.

[27497] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM668 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM668 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27498] As mentioned hereinabove with reference to Fig. 1, a function of VGAM668 gene, herein designated VGAM is inhibition of expression of VGAM668 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM668 correlate with, and may be deduced

from, the identity of the target genes which VGAM668 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27499] Golgi Complex Associated Protein 1, 60kDa (GOCAP1, Accession NM\_022735) is a VGAM668 host target gene. GOCAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GOCAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GOCAP1 BINDING SITE, designated SEQ ID:22940, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27500] A function of VGAM668 is therefore inhibition of Golgi Complex Associated Protein 1, 60kDa (GOCAP1, Accession NM\_022735). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GOCAP1. Leucine Zipper Transcription Factor-like 1 (LZTFL1, Accession NM\_020347) is another VGAM668 host target gene. LZTFL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

LZTFL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LZTFL1 BINDING SITE, designated SEQ ID:21598, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27501] Another function of VGAM668 is therefore inhibition of Leucine Zipper Transcription Factor-like 1 (LZTFL1, Accession NM\_020347). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LZTFL1. Solute Carrier Family 13 (sodium/sulfate symporters), Member 1 (SLC13A1, Accession NM\_022444) is another VGAM668 host target gene. SLC13A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC13A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC13A1 BINDING SITE, designated SEQ ID:22777, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27502] Another function of VGAM668 is therefore inhibition of Solute Carrier Family 13 (sodium/sulfate symporters), Member 1 (SLC13A1, Accession NM\_022444). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC13A1. DKFZp547I224 (Accession NM\_020221) is another VGAM668 host target gene. DKFZp547I224 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547I224, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547I224 BINDING SITE, designated SEQ ID:21475, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27503] Another function of VGAM668 is therefore inhibition of DKFZp547I224 (Accession NM\_020221). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547I224. FLJ12331 (Accession NM\_024986) is another VGAM668 host target gene. FLJ12331 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by FLJ12331, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12331 BINDING SITE, designated SEQ ID:24542, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27504] Another function of VGAM668 is therefore inhibition of FLJ12331 (Accession NM\_024986). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12331. FLJ20220 (Accession NM\_017718) is another VGAM668 host target gene. FLJ20220 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20220, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20220 BINDING SITE, designated SEQ ID:19304, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27505] Another function of VGAM668 is therefore inhibition of FLJ20220 (Accession NM\_017718). Accordingly, utilities of

VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20220. Oxysterol Binding Protein-like 3 (OSBPL3, Accession NM\_015550) is another VGAM668 host target gene. OSBPL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OSBPL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OSBPL3 BINDING SITE, designated SEQ ID:17820, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27506] Another function of VGAM668 is therefore inhibition of Oxysterol Binding Protein-like 3 (OSBPL3, Accession NM\_015550). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OSBPL3. TSPAN-3 (Accession NM\_005724) is another VGAM668 host target gene. TSPAN-3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSPAN-3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.



Table 2 illustrates the complementarity of the nucleotide sequences of TSPAN-3 BINDING SITE, designated SEQ ID:12277, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27507] Another function of VGAM668 is therefore inhibition of TSPAN-3 (Accession NM\_005724). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSPAN-3. LOC122830 (Accession XM\_058661) is another VGAM668 host target gene. LOC122830 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC122830, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC122830 BINDING SITE, designated SEQ ID:36707, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27508] Another function of VGAM668 is therefore inhibition of LOC122830 (Accession XM\_058661). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC122830. LOC138199 (Accession XM\_059950) is another VGAM668 host target gene. LOC138199 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC138199, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC138199 BINDING SITE, designated SEQ ID:37119, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27509] Another function of VGAM668 is therefore inhibition of LOC138199 (Accession XM\_059950). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC138199. LOC158357 (Accession XM\_088553) is another VGAM668 host target gene. LOC158357 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158357, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158357 BINDING SITE, designated SEQ ID:39821, to the nucleotide sequence of VGAM668 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3379.

[27510] Another function of VGAM668 is therefore inhibition of LOC158357 (Accession XM\_088553). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158357. LOC221687 (Accession XM\_166423) is another VGAM668 host target gene. LOC221687 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221687 BINDING SITE, designated SEQ ID:44309, to the nucleotide sequence of VGAM668 RNA, herein designated VGAM RNA, also designated SEQ ID:3379.

[27511] Another function of VGAM668 is therefore inhibition of LOC221687 (Accession XM\_166423). Accordingly, utilities of VGAM668 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221687. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 669 (VGAM669) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27512] VGAM669 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM669 was detected is described hereinabove with reference to Figs. 1–8.

[27513] VGAM669 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Yaba-like Disease Virus. VGAM669 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27514] VGAM669 gene encodes a VGAM669 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM669 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM669 precursor RNA is designated SEQ ID:655, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:655 is located at position 42333 relative to the genome of Yaba-like Disease Virus.

[27515] VGAM669 precursor RNA folds onto itself, forming

VGAM669 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27516] An enzyme complex designated DICER COMPLEX, `dices` the VGAM669 folded precursor RNA into VGAM669 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM669 RNA is designated SEQ ID:3380, and is provided hereinbelow with reference to the sequence listing part.

[27517] VGAM669 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM669 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM669 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27518] VGAM669 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM669 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM669 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM669 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM669 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27519] The complementary binding of VGAM669 RNA, herein designated VGAM RNA, to host target binding sites on VGAM669 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM669 host target RNA into VGAM669 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27520] It is appreciated that VGAM669 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM669 host target genes. The mRNA of each one of this plurality of VGAM669 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM669 RNA, herein designated VGAM RNA, and which when bound by VGAM669 RNA causes inhibition of translation of respective one or more VGAM669 host target proteins.

[27521] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM669 gene, herein designated VGAM GENE, on one or more VGAM669 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27522] It is yet further appreciated that a function of VGAM669 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM669 include diagnosis, prevention and treatment of viral infection by Yaba-like Disease Virus. Specific functions, and accordingly utilities, of VGAM669 correlate with, and may be deduced from, the identity of the host target genes which VGAM669 binds and inhibits,



and the function of these host target genes, as elaborated hereinbelow.

[27523] Nucleotide sequences of the VGAM669 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM669 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM669 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM669 are further described hereinbelow with reference to Table 1.

[27524] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM669 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM669 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27525] As mentioned hereinabove with reference to Fig. 1, a function of VGAM669 gene, herein designated VGAM is inhibition of expression of VGAM669 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM669 correlate with, and may be deduced from, the identity of the target genes which VGAM669 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[27526] Prion Protein (p27–30) (Creutzfeld–Jakob disease, Gerstmann–Strausler–Scheinker syndrome, fatal familial insomnia) (PRNP, Accession NM\_000311) is a VGAM669 host target gene. PRNP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PRNP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRNP BINDING SITE, designated SEQ ID:5849, to the nucleotide sequence of VGAM669 RNA, herein designated VGAM RNA, also designated SEQ ID:3380.

[27527] A function of VGAM669 is therefore inhibition of Prion Protein (p27–30) (Creutzfeld–Jakob disease, Gerstmann–Strausler–Scheinker syndrome, fatal familial insomnia) (PRNP, Accession NM\_000311), a gene which the function of prp is not known. prp is encoded in the host genome and is expressed both in normal and infected cells. Accordingly, utilities of VGAM669 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRNP. The function of PRNP has been established by previous studies. Mutations in the prion protein

gene are associated with Gerstmann–Straussler disease (GSD; 137440), Creutzfeldt–Jakob disease (CJD; 123400), and familial fatal insomnia (OMIM Ref. No. 600072), and aberrant isoforms of the prion protein can act as an infectious agent in these disorders as well as in kuru (OMIM Ref. No. 245300) and in scrapie in sheep. Riek et al. (1998) used the refined NMR structure of the mouse prion protein to investigate the structural basis of inherited human transmissible spongiform encephalopathies. In the cellular form of mouse prion protein, no spatial clustering of mutation sites was observed that would indicate the existence of disease–specific subdomains. A hydrogen bond between residues 128 and 178 provided a structural basis for the observed highly specific influence of a polymorphism at position 129 in human PRNP on the disease phenotype that segregates with the asp178–to–asn (D178N; 176640.0007) mutation. Overall, the NMR structure implied that only some of the disease–related amino acid replacements lead to reduced stability of the cellular form of PRNP, indicating that subtle structural differences in the mutant proteins may affect intermolecular signaling in a variety of different ways. Windl et al. (1999) searched for mutations and polymorphisms in the coding region of

the PRNP gene in 578 patients with suspect prion diseases referred to the German Creutzfeldt–Jakob disease surveillance unit over a period of 4.5 years. They found 40 cases with a missense mutation previously reported as pathogenic. Among these, the D178N mutation was the most common. In all of these cases, D178N was coupled with methionine at codon 129, resulting in the typical fatal familial insomnia genotype. Two novel missense mutations and several silent polymorphisms were found. In their Figure 1, Windl et al. (1999) diagrammed the known pathogenic mutations in the coding region of PRNP. Mead et al. (2001) analyzed the PRNP locus for tightly linked susceptibility factors for prion disease. They identified 56 polymorphic sites within 25 kb of the PRNP open reading frame, including sites within the PRNP promoter and the PRNP 3–prime untranslated region. These were characterized in 61 CEPH families, demonstrating extensive linkage disequilibrium around PRNP and the existence of 11 major European PRNP haplotypes. A common haplotype was overrepresented in patients with sporadic Creutzfeldt–Jakob disease. They could demonstrate that, in addition to the strong susceptibility conferred by codon 129, there was a significant independent association between spo–

radic CJD and a polymorphism upstream of PRNP. Although their sample size was necessarily small, no association was found between these polymorphisms and variant CJD or iatrogenic CJD, in keeping with their having distinct disease mechanisms. Cousens et al. (2001) described a cluster of variant CJD near the Leicestershire village of Queniborough in the U.K. Mead et al. (2001) could find no evidence of a PRNP founder susceptibility effect in that cluster. Animal model experiments lend further support to the function of PRNP. The incubation period and the neuropathology of transmissible spongiform encephalopathies have been extensively used to distinguish prion isolates (or strains) inoculated into panels of inbred mouse strains. Such studies have shown that the bovine spongiform encephalopathy (BSE) agent is indistinguishable from the agent causing variant Creutzfeldt-Jakob disease (vCJD), but differs from isolates of sporadic CJD, reinforcing the idea that the vCJD epidemic in Britain results from consumption of contaminated beef products. Manolakou et al. (2001) presented a mouse model for genetic and environmental factors that modify the incubation period of BSE cross-species transmission. They used 2 mouse strains that carried the same PrP allele, but dis-

played a 100-day difference in their mean incubation period following intracerebral inoculation with primary BSE isolate. They reported genetic effects on incubation period that map to 4 chromosomal regions in the mouse, and in addition they found significant factors of host environment, namely, the age of the host's mother, the age of the host at infection, and an interaction between the X chromosome and the cytoplasm in the host. Miele et al. (2002) identified 3 genes involved in mitochondrial physiology that were differentially expressed in the postnatal developing brains of normal mice and Prnp  $-/-$  mice. Further analysis showed that compared to the hippocampal CA1 regions of Prnp  $+/+$  mice, those of Prnp  $-/-$  mice contained 40% fewer mitochondria, unusual mitochondrial morphology, and significantly increased activity of mitochondrial manganese-dependent antioxidant superoxide dismutase (SOD2; 147460), suggesting greater levels of oxidative assault. These results suggested that there is a relationship between normal cellular PrP expression and quality and quantity of mitochondria.

[27528] It is appreciated that the abovementioned animal model for PRNP is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appre-

ciated from the publications sited hereinbelow.

[27529] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27530] Miele, G.; Jeffrey, M.; Turnbull, D.; Manson, J.; Clinton, M. : Ablation of cellular prion protein expression affects mitochondrial numbers and morphology. *Biochem. Biophys. Res. Commun.* 291: 372–377, 2002. ; and

[27531] Cousens, J.; Smith, P. G.; Ward, H.; Everington, D.; Knight, R. S. G.; Zeidler, M.; Stewart, G.; Smith–Bathgate, E. A. B.; Macleod, M.–A.; Mackenzie, J.; Will, R. G. : Geographical dis.

[27532] Further studies establishing the function and utilities of PRNP are found in John Hopkins OMIM database record ID 176640, and in cited publications numbered 51–52, 3735, 55–73, 75, 76–78, 3736, 12642–12651, 1655, 12652–12659, 357, 12660–12664, 5469, 5619–5643, 5708, 5712–5718, 5720, 5721–5723, 35 and 5724–5727 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tripartite Motif-containing 9 (TRIM9, Accession NM\_052978) is another VGAM669 host target gene. TRIM9 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TRIM9, corresponding to a HOST



TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM9 BINDING SITE, designated SEQ ID:27549, to the nucleotide sequence of VGAM669 RNA, herein designated VGAM RNA, also designated SEQ ID:3380.

[27533] Another function of VGAM669 is therefore inhibition of Tripartite Motif-containing 9 (TRIM9, Accession NM\_052978), a gene which may function as a positive regulator for mannosylphosphate transferase and is required to mediate mannosylphosphate transfer in both the core and outer chain portions of n-linked oligosaccharides. Accordingly, utilities of VGAM669 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM9. The function of TRIM9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74.pcnp (Accession NM\_020357) is another VGAM669 host target gene. pcnp BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by pcnp, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-

ble 2 illustrates the complementarity of the nucleotide sequences of pcnp BINDING SITE, designated SEQ ID:21627, to the nucleotide sequence of VGAM669 RNA, herein designated VGAM RNA, also designated SEQ ID:3380.

[27534] Another function of VGAM669 is therefore inhibition of pcnp (Accession NM\_020357). Accordingly, utilities of VGAM669 include diagnosis, prevention and treatment of diseases and clinical conditions associated with pcnp. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 670 (VGAM670) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27535] VGAM670 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM670 was detected is described hereinabove with reference to Figs. 1–8.

[27536] VGAM670 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Yaba-like Disease Virus. VGAM670 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27537] VGAM670 gene encodes a VGAM670 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM670 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM670 precursor RNA is designated SEQ ID:656, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:656 is located at position 116988 relative to the genome of Yaba-like Disease Virus.

[27538] VGAM670 precursor RNA folds onto itself, forming VGAM670 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27539] An enzyme complex designated DICER COMPLEX, `dices` the VGAM670 folded precursor RNA into VGAM670 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM670 RNA is designated SEQ ID:3381, and is provided hereinbelow with reference to the sequence listing part.

[27540] VGAM670 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM670 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM670 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27541] VGAM670 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM670 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM670 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM670 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM670 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27542] The complementary binding of VGAM670 RNA, herein designated VGAM RNA, to host target binding sites on VGAM670 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM670 host target RNA into VGAM670 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27543] It is appreciated that VGAM670 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM670 host target genes. The mRNA of each one of this plurality of VGAM670 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM670 RNA, herein designated VGAM RNA, and which when bound by VGAM670 RNA causes inhibition of translation of respective one or more VGAM670 host target proteins.

[27544] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM670 gene, herein designated VGAM GENE, on one or more VGAM670 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[27545] It is yet further appreciated that a function of VGAM670 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM670 include diagnosis, prevention and treatment of viral infection by Yaba-like Disease Virus. Specific functions, and accordingly utilities, of VGAM670 correlate with, and may be deduced from, the identity of the host target genes which VGAM670 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27546] Nucleotide sequences of the VGAM670 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM670 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM670 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM670 are further described hereinbelow with reference to Table 1.

[27547] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM670 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM670 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27548] As mentioned hereinabove with reference to Fig. 1, a function of VGAM670 gene, herein designated VGAM is inhibition of expression of VGAM670 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM670 correlate with, and may be deduced from, the identity of the target genes which VGAM670 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27549] Aldo-keto Reductase Family 1, Member D1 (delta 4-3-ketosteroid-5-beta-reductase) (AKR1D1, Accession NM\_005989) is a VGAM670 host target gene. AKR1D1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKR1D1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKR1D1 BINDING SITE, designated SEQ ID:12610, to the nucleotide sequence of VGAM670 RNA, herein designated VGAM RNA, also designated SEQ



ID:3381.

[27550] A function of VGAM670 is therefore inhibition of Aldo-keto Reductase Family 1, Member D1 (delta 4-3-ketosteroid-5-beta-reductase) (AKR1D1, Accession NM\_005989). Accordingly, utilities of VGAM670 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKR1D1. Reserved (C8orf13, Accession XM\_088377) is another VGAM670 host target gene. C8orf13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C8orf13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C8orf13 BINDING SITE, designated SEQ ID:39653, to the nucleotide sequence of VGAM670 RNA, herein designated VGAM RNA, also designated SEQ ID:3381.

[27551] Another function of VGAM670 is therefore inhibition of Reserved (C8orf13, Accession XM\_088377). Accordingly, utilities of VGAM670 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C8orf13. CED-6 (Accession NM\_016315) is another VGAM670 host target gene. CED-6 BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by CED-6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CED-6 BINDING SITE, designated SEQ ID:18431, to the nucleotide sequence of VGAM670 RNA, herein designated VGAM RNA, also designated SEQ ID:3381.

[27552] Another function of VGAM670 is therefore inhibition of CED-6 (Accession NM\_016315). Accordingly, utilities of VGAM670 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CED-6. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 671 (VGAM671) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27553] VGAM671 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM671 was detected is described hereinabove with reference to Figs. 1-8.

[27554] VGAM671 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Yaba-like Disease Virus. VGAM671 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27555] VGAM671 gene encodes a VGAM671 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM671 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM671 precursor RNA is designated SEQ ID:657, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:657 is located at position 134323 relative to the genome of Yaba-like Disease Virus.

[27556] VGAM671 precursor RNA folds onto itself, forming VGAM671 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27557] An enzyme complex designated DICER COMPLEX, `dices` the VGAM671 folded precursor RNA into VGAM671 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 85%) nucleotide sequence of VGAM671 RNA is designated SEQ ID:3382, and is provided hereinbelow with reference to the sequence listing part.

[27558] VGAM671 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM671 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM671 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27559] VGAM671 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM671 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM671 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM671 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM671 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27560] The complementary binding of VGAM671 RNA, herein designated VGAM RNA, to host target binding sites on VGAM671 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM671 host tar-

get RNA into VGAM671 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27561] It is appreciated that VGAM671 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM671 host target genes. The mRNA of each one of this plurality of VGAM671 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM671 RNA, herein designated VGAM RNA, and which when bound by VGAM671 RNA causes inhibition of translation of respective one or more VGAM671 host target proteins.

[27562] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM671 gene, herein designated VGAM GENE, on one or more VGAM671 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27563] It is yet further appreciated that a function of VGAM671 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM671 include diagnosis, prevention and treatment of viral infection by Yaba-like Disease Virus. Specific functions, and accordingly utilities, of VGAM671 correlate with, and may be deduced from, the identity of the host target genes which VGAM671 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27564] Nucleotide sequences of the VGAM671 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM671 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM671 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM671 are further

described hereinbelow with reference to Table 1.

[27565] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM671 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM671 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27566] As mentioned hereinabove with reference to Fig. 1, a function of VGAM671 gene, herein designated VGAM is inhibition of expression of VGAM671 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM671 correlate with, and may be deduced from, the identity of the target genes which VGAM671 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27567] Syntaxin 7 (STX7, Accession NM\_003569) is a VGAM671 host target gene. STX7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STX7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STX7 BINDING SITE, designated



SEQ ID:9624, to the nucleotide sequence of VGAM671 RNA, herein designated VGAM RNA, also designated SEQ ID:3382.

[27568] A function of VGAM671 is therefore inhibition of Syntaxin 7 (STX7, Accession NM\_003569). Accordingly, utilities of VGAM671 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STX7. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 672 (VGAM672) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27569] VGAM672 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM672 was detected is described hereinabove with reference to Figs. 1–8.

[27570] VGAM672 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Yaba-like Disease Virus. VGAM672 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27571] VGAM672 gene encodes a VGAM672 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM672 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM672 precursor RNA is designated SEQ ID:658, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:658 is located at position 134123 relative to the genome of Yaba-like Disease Virus.

[27572] VGAM672 precursor RNA folds onto itself, forming VGAM672 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27573] An enzyme complex designated DICER COMPLEX, `dices` the VGAM672 folded precursor RNA into VGAM672 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM672 RNA is designated SEQ ID:3383, and is provided hereinbelow with reference to the sequence listing part.

[27574] VGAM672 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM672 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM672 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27575] VGAM672 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM672 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM672 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM672 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM672 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27576] The complementary binding of VGAM672 RNA, herein designated VGAM RNA, to host target binding sites on VGAM672 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM672 host target RNA into VGAM672 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27577] It is appreciated that VGAM672 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM672 host target genes. The mRNA of each one of this plurality of VGAM672 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM672 RNA, herein designated VGAM RNA, and which when bound by VGAM672 RNA causes inhibition of translation of respective one or more VGAM672 host target proteins.

[27578] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM672 gene, herein designated VGAM GENE, on one or more VGAM672 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[27579] It is yet further appreciated that a function of VGAM672 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM672 include diagnosis, prevention and treatment of viral infection by Yaba-like Disease Virus. Specific functions, and accordingly utilities, of VGAM672 correlate with, and may be deduced from, the identity of the host target genes which VGAM672 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27580] Nucleotide sequences of the VGAM672 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM672 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM672 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM672 are further described hereinbelow with reference to Table 1.

[27581] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM672 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM672 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27582] As mentioned hereinabove with reference to Fig. 1, a function of VGAM672 gene, herein designated VGAM is inhibition of expression of VGAM672 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM672 correlate with, and may be deduced from, the identity of the target genes which VGAM672 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27583] SH2 Domain Containing Phosphatase Anchor Protein 1 (SPAP1, Accession NM\_030764) is a VGAM672 host target gene. SPAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPAP1 BINDING SITE, designated SEQ ID:25046, to the nucleotide sequence of VGAM672 RNA, herein designated VGAM RNA, also designated SEQ ID:3383.

[27584] A function of VGAM672 is therefore inhibition of SH2 Do-

main Containing Phosphatase Anchor Protein 1 (SPAP1, Accession NM\_030764), a gene which regulation of immunologic function. Accordingly, utilities of VGAM672 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPAP1. The function of SPAP1 has been established by previous studies. Davis et al. (2001) identified 2 BAC clones located at chromosome 1q21.1–q22. They found that one of these clones contained 3 novel putative Ig superfamily genes, which they designated FCRH1 (OMIM Ref. No. 606508), FCRH2, and FCRH3 (OMIM Ref. No. 606510), as well as 2 previously identified members of this family, FCRH4 (IRTA1; 605876) and FCRH5 (IRTA2; 605877). Sequence analysis predicted that the 508–amino acid type I transmembrane protein possesses a hydrophobic signal peptide, 4 extracellular C2 type Ig–like domains, 5 N–linked glycosylation sites, an uncharged transmembrane segment, and an 86–amino acid cytoplasmic tail with 1 ITAM (immunoreceptor tyrosine–based activation motif) and 2 ITIMs. Northern blot analysis revealed expression of approximately 3.0–, 4.4– and 5.5–kb transcripts chiefly in spleen and lymph nodes and a 2.4–kb transcript in kidney. RT–PCR analysis detected expression in mature B–cell lines. Davis et al.



(2001) suggested that FCRH2 may have an activating/inhibitory or a fine-tuning role in regulation of immunologic function

[27585] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27586] Davis, R. S.; Wang, Y.-H.; Kubagawa, H.; Cooper, M. D. : Identification of a family of Fc receptor homologs with preferential B cell expression. Proc. Nat. Acad. Sci. 98: 9772-9777, 2001. ; and

[27587] Xu, M.; Zhao, R.; Zhao, Z. J. : Molecular cloning and characterization of SPAP1, an inhibitory receptor. Biochem. Biophys. Res. Commun. 280: 768-775, 2001.

[27588] Further studies establishing the function and utilities of SPAP1 are found in John Hopkins OMIM database record ID 606509, and in cited publications numbered 6106-6107 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FENS-1 (Accession NM\_020830) is another VGAM672 host target gene. FENS-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FENS-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of FENS-1 BINDING SITE, designated SEQ ID:21891, to the nucleotide sequence of VGAM672 RNA, herein designated VGAM RNA, also designated SEQ ID:3383.

[27589] Another function of VGAM672 is therefore inhibition of FENS-1 (Accession NM\_020830). Accordingly, utilities of VGAM672 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FENS-1. FLJ20689 (Accession NM\_017972) is another VGAM672 host target gene. FLJ20689 BINDING SITE1 and FLJ20689 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ20689, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20689 BINDING SITE1 and FLJ20689 BINDING SITE2, designated SEQ ID:19703 and SEQ ID:19599 respectively, to the nucleotide sequence of VGAM672 RNA, herein designated VGAM RNA, also designated SEQ ID:3383.

[27590] Another function of VGAM672 is therefore inhibition of FLJ20689 (Accession NM\_017972). Accordingly, utilities of VGAM672 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ20689. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 674 (VGAM674) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27591] VGAM674 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM674 was detected is described hereinabove with reference to Figs. 1–8.

[27592] VGAM674 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM674 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27593] VGAM674 gene encodes a VGAM674 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM674 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM674 precursor RNA is designated SEQ ID:660, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:660 is located at position 10541 relative to the genome of Human Coronavirus 229E.

[27594] VGAM674 precursor RNA folds onto itself, forming VGAM674 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27595] An enzyme complex designated DICER COMPLEX, `dices` the VGAM674 folded precursor RNA into VGAM674 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM674 RNA is designated SEQ ID:3385, and is provided hereinbelow with reference to the sequence listing part.

[27596] VGAM674 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM674 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM674 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27597] VGAM674 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM674 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM674 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM674 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM674 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27598] The complementary binding of VGAM674 RNA, herein designated VGAM RNA, to host target binding sites on VGAM674 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM674 host target RNA into VGAM674 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27599] It is appreciated that VGAM674 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM674 host target genes. The mRNA of each one of this plurality of VGAM674 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM674 RNA, herein designated VGAM RNA, and which when bound by VGAM674 RNA causes in-

hibition of translation of respective one or more VGAM674 host target proteins.

[27600] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM674 gene, herein designated VGAM GENE, on one or more VGAM674 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27601] It is yet further appreciated that a function of VGAM674 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM674 include diagnosis, prevention and

treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM674 correlate with, and may be deduced from, the identity of the host target genes which VGAM674 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27602] Nucleotide sequences of the VGAM674 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM674 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM674 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM674 are further described hereinbelow with reference to Table 1.

[27603] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM674 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM674 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27604] As mentioned hereinabove with reference to Fig. 1, a function of VGAM674 gene, herein designated VGAM is inhibition of expression of VGAM674 target genes. It is



appreciated that specific functions, and accordingly utilities, of VGAM674 correlate with, and may be deduced from, the identity of the target genes which VGAM674 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27605] Diacylglycerol Kinase, Beta 90kDa (DGKB, Accession XM\_166516) is a VGAM674 host target gene. DGKB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DGKB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGKB BINDING SITE, designated SEQ ID:44450, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27606] A function of VGAM674 is therefore inhibition of Diacylglycerol Kinase, Beta 90kDa (DGKB, Accession XM\_166516), a gene which regulates the intracellular concentration of the second messenger diacylglycerol (DAG). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DGKB. The function of DGKB and its association with various diseases and clinical conditions, has

been established by previous studies, as described hereinabove with reference to VGAM497. Hepatocyte Growth Factor (hepapoietin A; scatter factor) (HGF, Accession XM\_168542) is another VGAM674 host target gene. HGF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HGF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HGF BINDING SITE, designated SEQ ID:45226, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27607] Another function of VGAM674 is therefore inhibition of Hepatocyte Growth Factor (hepapoietin A; scatter factor) (HGF, Accession XM\_168542), a gene which may be required for normal embryonic development; strongly similar to murine Hgf, has kringle domains. Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HGF. The function of HGF and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM174. Zinc Finger Protein 192 (ZNF192, Accession

NM\_006298) is another VGAM674 host target gene. ZNF192 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF192, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF192 BINDING SITE, designated SEQ ID:12991, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27608] Another function of VGAM674 is therefore inhibition of Zinc Finger Protein 192 (ZNF192, Accession NM\_006298). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF192. DKFZP434G1411 (Accession XM\_166383) is another VGAM674 host target gene. DKFZP434G1411 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434G1411, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434G1411 BINDING SITE, designated SEQ ID:44229, to the nucleotide sequence of

VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27609] Another function of VGAM674 is therefore inhibition of DKFZP434G1411 (Accession XM\_166383). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434G1411. DKFZP762D096 (Accession XM\_037662) is another VGAM674 host target gene. DKFZP762D096 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP762D096, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP762D096 BINDING SITE, designated SEQ ID:32664, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27610] Another function of VGAM674 is therefore inhibition of DKFZP762D096 (Accession XM\_037662). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP762D096. N4BP3 (Accession XM\_038920) is another VGAM674 host target gene. N4BP3 BINDING SITE

is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by N4BP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of N4BP3 BINDING SITE, designated SEQ ID:32943, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27611] Another function of VGAM674 is therefore inhibition of N4BP3 (Accession XM\_038920). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with N4BP3. LOC134637 (Accession XM\_059727) is another VGAM674 host target gene. LOC134637 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC134637, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC134637 BINDING SITE, designated SEQ ID:37079, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27612] Another function of VGAM674 is therefore inhibition of

LOC134637 (Accession XM\_059727). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC134637. LOC147622 (Accession XM\_097255) is another VGAM674 host target gene. LOC147622 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147622, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147622 BINDING SITE, designated SEQ ID:40850, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27613] Another function of VGAM674 is therefore inhibition of LOC147622 (Accession XM\_097255). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147622. LOC151361 (Accession XM\_098048) is another VGAM674 host target gene. LOC151361 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151361, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC151361 BINDING SITE, designated SEQ ID:41332, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27614] Another function of VGAM674 is therefore inhibition of LOC151361 (Accession XM\_098048). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151361. LOC152263 (Accession XM\_098195) is another VGAM674 host target gene. LOC152263 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152263, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152263 BINDING SITE, designated SEQ ID:41483, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27615] Another function of VGAM674 is therefore inhibition of LOC152263 (Accession XM\_098195). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152263. LOC51580 (Accession NM\_015874) is an-

other VGAM674 host target gene. LOC51580 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51580, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51580 BINDING SITE, designated SEQ ID:18018, to the nucleotide sequence of VGAM674 RNA, herein designated VGAM RNA, also designated SEQ ID:3385.

[27616] Another function of VGAM674 is therefore inhibition of LOC51580 (Accession NM\_015874). Accordingly, utilities of VGAM674 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51580. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 675 (VGAM675) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27617] VGAM675 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM675 was detected is described



hereinabove with reference to Figs. 1–8.

[27618] VGAM675 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM675 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27619] VGAM675 gene encodes a VGAM675 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM675 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM675 precursor RNA is designated SEQ ID:661, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:661 is located at position 12342 relative to the genome of Human Coronavirus 229E.

[27620] VGAM675 precursor RNA folds onto itself, forming VGAM675 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[27621] An enzyme complex designated DICER COMPLEX, `dices` the VGAM675 folded precursor RNA into VGAM675 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM675 RNA is designated SEQ ID:3386, and is provided hereinbelow with reference to the sequence listing part.

[27622] VGAM675 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM675 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM675 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27623] VGAM675 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM675 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM675 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM675 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM675 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27624] The complementary binding of VGAM675 RNA, herein designated VGAM RNA, to host target binding sites on VGAM675 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM675 host target RNA into VGAM675 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27625] It is appreciated that VGAM675 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM675 host target genes. The mRNA of each one of this plurality of VGAM675 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM675 RNA, herein designated VGAM RNA, and which when bound by VGAM675 RNA causes inhibition of translation of respective one or more VGAM675 host target proteins.

[27626] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM675 gene, herein designated VGAM GENE, on one or more VGAM675 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27627] It is yet further appreciated that a function of VGAM675 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM675 correlate with, and may be deduced from, the identity of the host target genes which VGAM675 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27628] Nucleotide sequences of the VGAM675 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM675 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM675 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM675 are further described hereinbelow with reference to Table 1.

[27629] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM675 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM675 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27630] As mentioned hereinabove with reference to Fig. 1, a function of VGAM675 gene, herein designated VGAM is inhibition of expression of VGAM675 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM675 correlate with, and may be deduced from, the identity of the target genes which VGAM675 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27631] A Disintegrin and Metalloproteinase Domain 12 (meltrin alpha) (ADAM12, Accession NM\_003474) is a VGAM675 host target gene. ADAM12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAM12, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM12 BINDING SITE, designated SEQ ID:9543, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27632] A function of VGAM675 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 12 (meltrin alpha) (ADAM12, Accession NM\_003474), a gene which involved in skeletal muscle regeneration, specifically at the onset of cell fusion. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM12. The function of ADAM12 has been established by previous studies. To isolate genes related to fertilin expressed in muscle, Yagami-Hiromasa et al. (1995) amplified cDNAs prepared from a mouse myogenic cell line by PCR using degenerative primers for conserved amino acids between fertilin-alpha and -beta (OMIM Ref. No. 601533). They identified 3 novel mouse sequences, which they called meltrins. Similarly to myogenin, a marker of early muscle differentiation, mouse meltrin-alpha is expressed in neonatal muscle and bone, and its expression increases dramatically in

response to the induction of differentiation. Immunocytochemical localization and functional expression studies suggested that meltrin- $\alpha$  may be involved in myotube formation. Galliano et al. (2000) found by RT-PCR and immunoblot analyses that expression of mouse Adam12 increases during muscle regeneration, while the levels of other ADAMs remain constant. Immunofluorescence analysis revealed staining of small, newly formed muscle fibers in regenerating but not normal adult muscle cells. Using a yeast 2-hybrid screen of a human skeletal muscle cDNA library with the cytoplasmic tail of human ADAM12 as bait, Galliano et al. (2000) determined that the membrane proximal portion of the C-terminal half of myristoylated ADAM12 interacts with muscle-specific  $\alpha$ -actinin-2 (ACTN2; 102573). Galliano et al. (2000) determined that overexpression of cytosolic ADAM12 containing the ACTN2-binding site inhibits mouse myoblast fusion.

[27633] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27634] Galliano, M.-F.; Huet, C.; Frygeliuss, J.; Polgren, A.; Wewer, U. M.; Engvall, E. : Binding of ADAM12, a marker of skele-



tal muscle regeneration, to the muscle-specific actin-binding protein, alpha-actinin-2, is required for myoblast fusion. J. Biol. Chem. 275: 13933-13939, 2000. ; and

[27635] Yagami-Hiromasa, T.; Sato, T.; Kurisaki, T.; Kamijo, K.; Nabeshima, Y.; Fujisawa-Sehara, A. : A metalloprotease-disintegrin participating in myoblast fusion. Nature 377: 652-656, 1995.

[27636] Further studies establishing the function and utilities of ADAM12 are found in John Hopkins OMIM database record ID 602714, and in cited publications numbered 1124-1126 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Arachidonate 12-lipoxygenase, 12R Type (ALOX12B, Accession NM\_001139) is another VGAM675 host target gene. ALOX12B BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ALOX12B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALOX12B BINDING SITE, designated SEQ ID:6807, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27637] Another function of VGAM675 is therefore inhibition of Arachidonate 12-lipoxygenase, 12R Type (ALOX12B, Accession NM\_001139), a gene which converts arachidonic acid to 12r- hydroperoxyeicosatetraenoic acid (12r-hpETE). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALOX12B. The function of ALOX12B has been established by previous studies. 12R-lipoxygenase catalyzes the conversion of arachidonic acid to 12R-hydroxyeicosatetraenoic acid (12R-HETE). In a database search for novel lipoxygenases, Sun et al. (1998) identified a novel lipoxygenase gene. The cDNA encoded a 701-amino acid polypeptide which when expressed produced a protein with specific 12R-lipoxygenase activity. By RT-PCR, but not by Northern blot analysis, Sun et al. (1998) detected 12R-lipoxygenase mRNA in B cells and adult skin. Boeglin et al. (1998) also cloned the ALOX12B gene. The ALOX12B cDNA showed the greatest sequence similarity to the second type of human 15S-lipoxygenase (ALOX15B; 603697), and was more distantly related to human 12S-lipoxygenase (ALOX12; 152391). They showed that ALOX12B is expressed in keratinocytes and psoriatic scales, but they were not able to detect any tran-

scription of the gene on several multiple-tissue Northern blots. Boeglin et al. (1998) provided mechanistic evidence for a lipoxygenase route to 12R-HETE in human psoriatic tissue and described a 12R-lipoxygenase that could account for the biosynthesis.

[27638] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27639] Boeglin, W. E.; Kim, R. B.; Brash, A. R. : A 12R-lipoxygenase in human skin: mechanistic evidence, molecular cloning, and expression. Proc. Nat. Acad. Sci. 95: 6744-6749, 1998. ; and

[27640] Jobard, F.; Lefevre, C.; Karaduman, A.; Blanchet-Bardon, C.; Emre, S.; Weissenbach, J.; Ozguc, M.; Lathrop, M.; Prud'homme, J.-F.; Fischer, J. : Lipoxygenase-3 (ALOXE3) and 12(R)-lipoxy.

[27641] Further studies establishing the function and utilities of ALOX12B are found in John Hopkins OMIM database record ID 603741, and in cited publications numbered 289 and 9437 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ASH1 (Accession NM\_018489) is another VGAM675 host target gene. ASH1 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by ASH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASH1 BINDING SITE, designated SEQ ID:20548, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27642] Another function of VGAM675 is therefore inhibition of ASH1 (Accession NM\_018489), a gene which is a candidate regulator of development in the mammalian central nervous system and neural crest. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASH1. The function of ASH1 has been established by previous studies. Using retroviral labeling in organotypic slice cultures of the embryonic human forebrain, Letinic et al. (2002) demonstrated the existence of 2 distinct lineages of neocortical GABAergic neurons. One lineage expresses DLX1 (OMIM Ref. No. 600029) and DLX2 (OMIM Ref. No. 126255) and MASH1 transcription factors, represents 65% of neocortical GABAergic neurons in humans, and originates from MASH1-expressing progenitors of the neocor-

tical ventricular and subventricular zone of the dorsal forebrain. The second lineage, characterized by the expression of DLX1 and DLX2 but not MASH1, forms around 35% of the GABAergic neurons and originates from the ganglionic eminence of the ventral forebrain. Letinic et al. (2002) suggested that modifications in the expression pattern of transcription factors in the forebrain may underlie species-specific programs for the generation of neocortical local circuit neurons and that distinct lineages of cortical interneurons may be differentially affected in genetic and acquired diseases of the human brain. Animal model experiments lend further support to the function of MASH1. By homologous recombination in embryonic stem cells, Guillemot et al. (1993) created a null allele of the Mash1 gene. Homozygous mice died at birth with apparent breathing and feeding defects. The brain and spinal cord appeared normal, but the olfactory epithelium and sympathetic, parasympathetic, and enteric ganglia were severely affected. These observations suggested that the Mash1 gene, like its *Drosophila* homologs, controls a basic operation in development of neuronal progenitors in distinct neural lineages.

[27643] It is appreciated that the abovementioned animal model

for ASH1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[27644] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27645] Letinic, K.; Zoncu, R.; Rakic, P. : Origin of GABAergic neurons in the human neocortex. *Nature* 417: 645–649, 2002. ; and

[27646] Guillemot, F.; Lo, L.-C.; Johnson, J. E.; Auerbach, A.; Anderson, D. J.; Joyner, A. L. : Mammalian achaete-scute homolog 1 is required for the early development of olfactory and autonom.

[27647] Further studies establishing the function and utilities of ASH1 are found in John Hopkins OMIM database record ID 100790, and in cited publications numbered 12331–1233 and 12762 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ATP Synthase, H<sup>+</sup> Transporting, Mitochondrial F<sub>0</sub> Complex, Subunit F6 (ATP5J, Accession NM\_001685) is another VGAM675 host target gene. ATP5J BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ATP5J, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP5J BINDING SITE, designated SEQ ID:7408, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27648] Another function of VGAM675 is therefore inhibition of ATP Synthase, H<sup>+</sup> Transporting, Mitochondrial F0 Complex, Subunit F6 (ATP5J, Accession NM\_001685), a gene which is one of the chains of the nonenzymatic component of the mitochondrial ATPase complex. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP5J. The function of ATP5J and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM556.DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide, Y Chromosome (DBY, Accession NM\_004660) is another VGAM675 host target gene. DBY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DBY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of DBY BINDING SITE, designated SEQ ID:11026, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27649] Another function of VGAM675 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide, Y Chromosome (DBY, Accession NM\_004660), a gene which plays a key role in the spermatogenic process. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DBY. The function of DBY and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM374. Hexokinase 1 (HK1, Accession NM\_033497) is another VGAM675 host target gene. HK1 BINDING SITE1 through HK1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HK1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HK1 BINDING SITE1 through HK1 BINDING SITE3, designated SEQ ID:27269, SEQ ID:27272 and SEQ ID:27275 respectively, to the nu-



cleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27650] Another function of VGAM675 is therefore inhibition of Hexokinase 1 (HK1, Accession NM\_033497). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HK1. KiSS-1 Metastasis-suppressor (KISS1, Accession NM\_002256) is another VGAM675 host target gene. KISS1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KISS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KISS1 BINDING SITE, designated SEQ ID:8061, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27651] Another function of VGAM675 is therefore inhibition of KiSS-1 Metastasis-suppressor (KISS1, Accession NM\_002256), a gene which suppresses metastases of melanomas and breast carcinomas without affecting tumorigenicity. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KISS1. The function of KISS1

has been established by previous studies. Welch et al. (1994) found that microcell-mediated transfer of human chromosome 6 into human metastatic melanoma cells (C8161 or MelJuSo) suppressed their ability to metastasize in athymic nude mice by at least 95% without affecting the tumorigenicity of the cells. Using a modified subtractive hybridization approach, Lee et al. (1996) isolated a cDNA expressed in hybrid chromosome 6-C8161 cells but not in parental C8161 cells. They designated the cDNA KISS1, combining laboratory nomenclature for putative suppressor sequences with acknowledgment of the gene's discovery in Hershey, Pennsylvania. Lee et al. (1996) reported the sequence of the predicted KISS1 protein and a corrected sequence in a published erratum. The KISS1 protein consists of 145 amino acids. Northern blot analysis revealed that KISS1 was expressed as a 1-kb mRNA in chromosome 6-C8161 hybrid cell lines as well as in normal placenta tissue. Low levels of smaller transcripts were observed in pancreas and kidney. Lee et al. (1996) did not detect KISS1 expression in any cell line capable of metastasizing in athymic nude mice.

[27652] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [27653] Lee, J.-H.; Welch, D. R. : Suppression of metastasis in human breast carcinoma MDA-MB-435 cells after transfection with the metastasis suppressor gene, KiSS-1. *Cancer Res.* 57: 2384-2387, 1997. ; and
- [27654] Ohtaki, T.; Shintani, Y.; Honda, S.; Matsumoto, H.; Hori, A.; Kanehashi, K.; Terao, Y.; Kumano, S.; Takatsu, Y.; Masuda, Y.; Ishibashi, Y.; Watanabe, T.; and 9 others : Metastasis suppr.
- [27655] Further studies establishing the function and utilities of KISS1 are found in John Hopkins OMIM database record ID 603286, and in cited publications numbered 5276-5280 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540) is another VGAM675 host target gene. ODF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ODF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ODF2 BINDING SITE, designated SEQ ID:8387, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3386.

[27656] Another function of VGAM675 is therefore inhibition of Outer Dense Fiber of Sperm Tails 2 (ODF2, Accession NM\_002540), a gene which is very strongly similar to rat Odf2 . Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ODF2. The function of ODF2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM363. Pyrimidinergic Receptor P2Y, G-protein Coupled, 6 (P2RY6, Accession NM\_004154) is another VGAM675 host target gene. P2RY6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by P2RY6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P2RY6 BINDING SITE, designated SEQ ID:10354, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27657] Another function of VGAM675 is therefore inhibition of Pyrimidinergic Receptor P2Y, G-protein Coupled, 6

(P2RY6, Accession NM\_004154), a gene which mediates cellular responses to nucleotides. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P2RY6. The function of P2RY6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM445. Protein Phosphatase 2 (formerly 2A), Regulatory Subunit B (PR 52), Beta Isoform (PPP2R2B, Accession NM\_004576) is another VGAM675 host target gene. PPP2R2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2R2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R2B BINDING SITE, designated SEQ ID:10922, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27658] Another function of VGAM675 is therefore inhibition of Protein Phosphatase 2 (formerly 2A), Regulatory Subunit B (PR 52), Beta Isoform (PPP2R2B, Accession NM\_004576). Accordingly, utilities of VGAM675 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with PPP2R2B. Protein Phosphatase 2, Regulatory Subunit B (B56), Alpha Isoform (PPP2R5A, Accession NM\_006243) is another VGAM675 host target gene.

PPP2R5A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2R5A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R5A BINDING SITE, designated SEQ ID:12908, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27659] Another function of VGAM675 is therefore inhibition of Protein Phosphatase 2, Regulatory Subunit B (B56), Alpha Isoform (PPP2R5A, Accession NM\_006243), a gene which is a regulatory subunit of protein phosphatase 2A. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R5A. The function of PPP2R5A has been established by previous studies. Protein phosphorylation is a regulatory mechanism commonly employed in cellular processes such as cell cycle progression, growth factor

signaling, and cell transformation. Protein phosphatase 2A (PP2A), a heterotrimeric serine/threonine phosphatase, has been implicated in a variety of regulatory processes including cell growth and division, muscle contraction, and gene transcription. PP2A is a trimeric enzyme composed of a catalytic subunit (OMIM Ref. No. 176915), a structural subunit, and any of several different regulatory subunits which control its specificity. One family of related PP2A regulatory subunits is designated the B56 family and contains at least 5 different members (McCright and Virshup (1995)). The alpha subunit gene encodes a cytoplasmic phosphoprotein. The alpha and gamma (OMIM Ref. No. 601645) subunits are expressed at highest levels in skeletal and cardiac muscle. See also the entries describing the beta (OMIM Ref. No. 601644), delta (OMIM Ref. No. 601646), and epsilon (OMIM Ref. No. 601647) subunits. McCright et al. (1996) mapped the gene for the alpha subunit, designated PPP2R5A, to 1q41 by fluorescence in situ hybridization.

[27660] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27661] McCright, B.; Brothman, A. R.; Virshup, D. M. : Assignment

of human protein phosphatase 2A regulatory subunit genes B56-alpha, B56-beta, B56-gamma, B56-delta, and B56-epsilon (PPP2R5A--PPP2R5E), highly expressed in muscle and brain, to chromosome regions 1q41, 11q12, 3p21, 6p21.1, and 7p11.2-to-p12. Genomics 36: 168-170, 1996. ; and

[27662] McCright, B.; Virshup, D. M. : Identification of a new family of protein phosphatase 2A regulatory subunits. J. Biol. Chem. 270: 26123-26128, 1995.

[27663] Further studies establishing the function and utilities of PPP2R5A are found in John Hopkins OMIM database record ID 601643, and in cited publications numbered 6687-6688 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SNL (Accession NM\_003088) is another VGAM675 host target gene. SNL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SNL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNL BINDING SITE, designated SEQ ID:9066, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.



[27664] Another function of VGAM675 is therefore inhibition of SNL (Accession NM\_003088), a gene which organizes filamentous actin into bundles with a minimum of 4.1:1 actin/fascin ratio. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNL. The function of SNL has been established by previous studies. Sea urchin fascin, one of the first actin-bundling proteins extensively characterized, can crosslink actin filaments in vitro (Bryan and Kane, 1982). The cloning of a fascin cDNA by Bryan et al. (1993) showed that fascin is homologous to the *Drosophila* singed gene product. Duh et al. (1994) isolated cDNAs encoding the human homolog of sea urchin fascin and *Drosophila* singed, called HSN by them, from a human teratocarcinoma cDNA library. The HSN mRNA was expressed at various levels in all human tissues analyzed, and it was highly expressed in actively growing renal carcinoma cell lines and in activated but not in resting lymphocytes, suggesting a functional role for HSN in proliferation. The HSN gene is predicted to encode a 493-amino acid protein with a molecular mass of 55 kD. Based on peptide sequence identity and immunocrossreactivity, Duh et al. (1994) indicated that the HSN protein is the 55-kD

actin-bundling protein purified from HeLa cells (Yamashiro-Matsumura and Matsumura, 1985). This HeLa cell-derived 55-kD protein is thought to be involved in the assembly of actin filament bundles present in microspikes, membrane ruffles, and stress fibers (Yamashiro-Matsumura and Matsumura, 1986). Using immunohistochemistry, Pinkus et al. (1997) found that nearly all Reed-Sternberg cells in Hodgkin disease (OMIM Ref. No. 236000), except in the nodular lymphocyte predominance type, express fascin. They proposed that fascin expression may be helpful in distinguishing Hodgkin from non-Hodgkin lymphoma and suggested that Reed-Sternberg cells may have a dendritic cell derivation.

[27665] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27666] Pinkus, G. S.; Pinkus, J. L.; Langhoff, E.; Matsumura, F.; Yamashiro, S.; Mosialos, G.; Said, J. W. : Fascin, a sensitive new marker for Reed-Sternberg cells of Hodgkin's disease: evidence for a dendritic or B cell derivation? *Am. J. Path.* 150: 543-562, 1997. ; and

[27667] Sonderbye, L.; Magerstadt, R.; Blatman, R. N.; Preffer, F. I.;

Langhoff, E. : Selective expression of human fascin (p55) by dendritic leukocytes. Adv. Exp. Med. Biol. 471: 41–46, 1997.

[27668] Further studies establishing the function and utilities of SNL are found in John Hopkins OMIM database record ID 602689, and in cited publications numbered 544 and 7640–7647 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. TEM7 (Accession NM\_020405) is another VGAM675 host target gene. TEM7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TEM7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TEM7 BINDING SITE, designated SEQ ID:21669, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27669] Another function of VGAM675 is therefore inhibition of TEM7 (Accession NM\_020405), a gene which involves in angiogenesis. Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TEM7. The function of TEM7 and its association with various diseases and clinical

conditions, has been established by previous studies, as described hereinabove with reference to VGAM23.F-box Only Protein 27 (FBXO27, Accession XM\_059045) is another VGAM675 host target gene. FBXO27 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FBXO27, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO27 BINDING SITE, designated SEQ ID:36838, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27670] Another function of VGAM675 is therefore inhibition of F-box Only Protein 27 (FBXO27, Accession XM\_059045). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXO27. FLJ10521 (Accession NM\_018125) is another VGAM675 host target gene. FLJ10521 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10521, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

FLJ10521 BINDING SITE, designated SEQ ID:19911, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27671] Another function of VGAM675 is therefore inhibition of FLJ10521 (Accession NM\_018125). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10521. Hepatitis B Virus X Associated Protein (HBXAP, Accession NM\_016578) is another VGAM675 host target gene. HBXAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HBXAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HBXAP BINDING SITE, designated SEQ ID:18656, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27672] Another function of VGAM675 is therefore inhibition of Hepatitis B Virus X Associated Protein (HBXAP, Accession NM\_016578). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HBXAP. Histamine Receptor

H4 (HRH4, Accession NM\_021624) is another VGAM675 host target gene. HRH4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HRH4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HRH4 BINDING SITE, designated SEQ ID:22257, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27673] Another function of VGAM675 is therefore inhibition of Histamine Receptor H4 (HRH4, Accession NM\_021624). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HRH4. KIAA0089 (Accession XM\_046056) is another VGAM675 host target gene. KIAA0089 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0089, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0089 BINDING SITE, designated SEQ ID:34666, to the nucleotide sequence of VGAM675 RNA, herein designated

VGAM RNA, also designated SEQ ID:3386.

[27674] Another function of VGAM675 is therefore inhibition of KIAA0089 (Accession XM\_046056). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0089. KIAA0547 (Accession NM\_014793) is another VGAM675 host target gene. KIAA0547 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0547, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0547 BINDING SITE, designated SEQ ID:16695, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27675] Another function of VGAM675 is therefore inhibition of KIAA0547 (Accession NM\_014793). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0547. KIAA1318 (Accession XM\_041080) is another VGAM675 host target gene. KIAA1318 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1318, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1318 BINDING SITE, designated SEQ ID:33429, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27676] Another function of VGAM675 is therefore inhibition of KIAA1318 (Accession XM\_041080). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1318. MGC16175 (Accession NM\_032765) is another VGAM675 host target gene. MGC16175 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC16175, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC16175 BINDING SITE, designated SEQ ID:26511, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27677] Another function of VGAM675 is therefore inhibition of MGC16175 (Accession NM\_032765). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with MGC16175. PRO1866 (Accession NM\_018510) is another VGAM675 host target gene. PRO1866 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO1866, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1866 BINDING SITE, designated SEQ ID:20580, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27678] Another function of VGAM675 is therefore inhibition of PRO1866 (Accession NM\_018510). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1866. Williams Beuren Syndrome Chromosome Region 22 (WBSCR22, Accession NM\_017528) is another VGAM675 host target gene. WBSCR22 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by WBSCR22, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WBSCR22 BINDING SITE,

designated SEQ ID:18971, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27679] Another function of VGAM675 is therefore inhibition of Williams Beuren Syndrome Chromosome Region 22 (WBSCR22, Accession NM\_017528). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WBSCR22. Zinc Finger Protein 230 (ZNF230, Accession NM\_006300) is another VGAM675 host target gene. ZNF230 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZNF230, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF230 BINDING SITE, designated SEQ ID:12994, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27680] Another function of VGAM675 is therefore inhibition of Zinc Finger Protein 230 (ZNF230, Accession NM\_006300). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with ZNF230. LOC145989 (Accession XM\_004815) is another VGAM675 host target gene. LOC145989 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145989, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145989 BINDING SITE, designated SEQ ID:29954, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27681] Another function of VGAM675 is therefore inhibition of LOC145989 (Accession XM\_004815). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145989. LOC148018 (Accession XM\_092020) is another VGAM675 host target gene. LOC148018 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148018, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148018 BINDING SITE, designated SEQ ID:40090, to

the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27682] Another function of VGAM675 is therefore inhibition of LOC148018 (Accession XM\_092020). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148018. LOC148223 (Accession XM\_086101) is another VGAM675 host target gene. LOC148223 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148223, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148223 BINDING SITE, designated SEQ ID:38494, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27683] Another function of VGAM675 is therefore inhibition of LOC148223 (Accession XM\_086101). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148223. LOC158401 (Accession XM\_088568) is another VGAM675 host target gene. LOC158401 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC158401, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158401 BINDING SITE, designated SEQ ID:39836, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27684] Another function of VGAM675 is therefore inhibition of LOC158401 (Accession XM\_088568). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158401. LOC203378 (Accession XM\_117541) is another VGAM675 host target gene. LOC203378 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203378, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203378 BINDING SITE, designated SEQ ID:43549, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27685] Another function of VGAM675 is therefore inhibition of LOC203378 (Accession XM\_117541). Accordingly, utilities

of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203378. LOC220549 (Accession XM\_167521) is another VGAM675 host target gene. LOC220549 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC220549, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220549 BINDING SITE, designated SEQ ID:44648, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27686] Another function of VGAM675 is therefore inhibition of LOC220549 (Accession XM\_167521). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220549. LOC221490 (Accession XM\_168084) is another VGAM675 host target gene. LOC221490 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221490, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC221490 BINDING SITE, designated SEQ ID:44985, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27687] Another function of VGAM675 is therefore inhibition of LOC221490 (Accession XM\_168084). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221490. LOC255146 (Accession XM\_170985) is another VGAM675 host target gene. LOC255146 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255146, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255146 BINDING SITE, designated SEQ ID:45755, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27688] Another function of VGAM675 is therefore inhibition of LOC255146 (Accession XM\_170985). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255146. LOC255452 (Accession XM\_174088) is another VGAM675 host target gene. LOC255452 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC255452, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255452 BINDING SITE, designated SEQ ID:46576, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27689] Another function of VGAM675 is therefore inhibition of LOC255452 (Accession XM\_174088). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255452. LOC257000 (Accession XM\_172999) is another VGAM675 host target gene. LOC257000 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC257000, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257000 BINDING SITE, designated SEQ ID:46271, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27690] Another function of VGAM675 is therefore inhibition of



LOC257000 (Accession XM\_172999). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257000. LOC90785 (Accession XM\_034110) is another VGAM675 host target gene. LOC90785 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90785, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90785 BINDING SITE, designated SEQ ID:32005, to the nucleotide sequence of VGAM675 RNA, herein designated VGAM RNA, also designated SEQ ID:3386.

[27691] Another function of VGAM675 is therefore inhibition of LOC90785 (Accession XM\_034110). Accordingly, utilities of VGAM675 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90785. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 676 (VGAM676) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[27692] VGAM676 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM676 was detected is described hereinabove with reference to Figs. 1–8.

[27693] VGAM676 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM676 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27694] VGAM676 gene encodes a VGAM676 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM676 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM676 precursor RNA is designated SEQ ID:662, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:662 is located at position 13267 relative to the genome of Human Coronavirus 229E.

[27695] VGAM676 precursor RNA folds onto itself, forming VGAM676 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[27696] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM676 folded precursor RNA into VGAM676 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 48%) nucleotide se-  
quence of VGAM676 RNA is designated SEQ ID:3387, and  
is provided hereinbelow with reference to the sequence  
listing part.

[27697] VGAM676 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM676 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM676 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[27698] VGAM676 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM676 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM676 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM676 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM676 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[27699] The complementary binding of VGAM676 RNA, herein designated VGAM RNA, to host target binding sites on VGAM676 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM676 host target RNA into VGAM676 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27700] It is appreciated that VGAM676 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM676 host target genes. The mRNA of each one of this plurality of VGAM676 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM676 RNA, herein designated VGAM RNA, and which when bound by VGAM676 RNA causes inhibition of translation of respective one or more VGAM676 host target proteins.

[27701] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM676 gene, herein designated VGAM GENE, on one or

more VGAM676 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27702] It is yet further appreciated that a function of VGAM676 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM676 correlate with, and may be deduced from, the identity of the host target genes which VGAM676 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [27703] Nucleotide sequences of the VGAM676 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM676 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM676 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM676 are further described hereinbelow with reference to Table 1.
- [27704] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM676 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM676 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [27705] As mentioned hereinabove with reference to Fig. 1, a function of VGAM676 gene, herein designated VGAM is inhibition of expression of VGAM676 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM676 correlate with, and may be deduced from, the identity of the target genes which VGAM676 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [27706] Fatty-acid-Coenzyme A Ligase, Long-chain 5 (FACL5, Ac-

cession XM\_034424) is a VGAM676 host target gene. FACL5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FACL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FACL5 BINDING SITE, designated SEQ ID:32105, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27707] A function of VGAM676 is therefore inhibition of Fatty-acid-Coenzyme A Ligase, Long-chain 5 (FACL5, Accession XM\_034424), a gene which may be involved in fatty acid metabolism; contains an AMP-binding domain. Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FACL5. The function of FACL5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM357. Frizzled Homolog 10 (Drosophila) (FZD10, Accession NM\_007197) is another VGAM676 host target gene. FZD10 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region



of mRNA encoded by FZD10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FZD10 BINDING SITE, designated SEQ ID:14049, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27708] Another function of VGAM676 is therefore inhibition of Frizzled Homolog 10 (Drosophila) (FZD10, Accession NM\_007197). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FZD10. Transforming, Acidic Coiled-coil Containing Protein 1 (TACC1, Accession NM\_006283) is another VGAM676 host target gene. TACC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TACC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TACC1 BINDING SITE, designated SEQ ID:12959, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27709] Another function of VGAM676 is therefore inhibition of Transforming, Acidic Coiled-coil Containing Protein 1 (TACC1, Accession NM\_006283). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TACC1. Wolf-Hirschhorn Syndrome Candidate 1 (WHSC1, Accession NM\_133333) is another VGAM676 host target gene. WHSC1 BINDING SITE1 through WHSC1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by WHSC1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WHSC1 BINDING SITE1 through WHSC1 BINDING SITE3, designated SEQ ID:28457, SEQ ID:28472 and SEQ ID:28440 respectively, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27710] Another function of VGAM676 is therefore inhibition of Wolf-Hirschhorn Syndrome Candidate 1 (WHSC1, Accession NM\_133333), a gene which binds covalently to and repairs g/t mismatches. Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WHSC1. The func-

tion of WHSC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200.DEPP (Accession NM\_007021) is another VGAM676 host target gene. DEPP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DEPP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DEPP BINDING SITE, designated SEQ ID:13876, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27711] Another function of VGAM676 is therefore inhibition of DEPP (Accession NM\_007021). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DEPP. DKFZP761I2123 (Accession NM\_031449) is another VGAM676 host target gene. DKFZP761I2123 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP761I2123, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates

the complementarity of the nucleotide sequences of DKFZP761I2123 BINDING SITE, designated SEQ ID:25462, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27712] Another function of VGAM676 is therefore inhibition of DKFZP761I2123 (Accession NM\_031449). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP761I2123. FLJ14768 (Accession NM\_032836) is another VGAM676 host target gene. FLJ14768 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14768, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14768 BINDING SITE, designated SEQ ID:26616, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27713] Another function of VGAM676 is therefore inhibition of FLJ14768 (Accession NM\_032836). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14768. GMPPB (Accession XM\_171044) is another VGAM676 host

target gene. GMPPB BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by GMPPB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GMPPB BINDING SITE, designated SEQ ID:45815, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27714] Another function of VGAM676 is therefore inhibition of GMPPB (Accession XM\_171044). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GMPPB. KIAA0335 (Accession NM\_014803) is another VGAM676 host target gene. KIAA0335 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0335, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0335 BINDING SITE, designated SEQ ID:16730, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27715] Another function of VGAM676 is therefore inhibition of KIAA0335 (Accession NM\_014803). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0335. KIAA1553 (Accession XM\_166320) is another VGAM676 host target gene. KIAA1553 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1553, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1553 BINDING SITE, designated SEQ ID:44141, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27716] Another function of VGAM676 is therefore inhibition of KIAA1553 (Accession XM\_166320). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1553. Rpo1-2 (Accession NM\_019014) is another VGAM676 host target gene. Rpo1-2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by Rpo1-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Rpo1-2 BINDING SITE, designated SEQ ID:21101, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27717] Another function of VGAM676 is therefore inhibition of Rpo1-2 (Accession NM\_019014). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rpo1-2. Solute Carrier Family 17 (sodium-dependent inorganic phosphate cotransporter), Member 6 (SLC17A6, Accession NM\_020346) is another VGAM676 host target gene. SLC17A6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC17A6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC17A6 BINDING SITE, designated SEQ ID:21593, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27718] Another function of VGAM676 is therefore inhibition of Solute Carrier Family 17 (sodium-dependent inorganic

phosphate cotransporter), Member 6 (SLC17A6, Accession NM\_020346). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC17A6. LOC143392 (Accession XM\_096423) is another VGAM676 host target gene. LOC143392 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC143392, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143392 BINDING SITE, designated SEQ ID:40357, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27719] Another function of VGAM676 is therefore inhibition of LOC143392 (Accession XM\_096423). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143392. LOC148189 (Accession XM\_086087) is another VGAM676 host target gene. LOC148189 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148189, corresponding to a HOST TARGET binding site such as BIND-



ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148189 BINDING SITE, designated SEQ ID:38482, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27720] Another function of VGAM676 is therefore inhibition of LOC148189 (Accession XM\_086087). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148189. LOC149271 (Accession XM\_086475) is another VGAM676 host target gene. LOC149271 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149271, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149271 BINDING SITE, designated SEQ ID:38678, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27721] Another function of VGAM676 is therefore inhibition of LOC149271 (Accession XM\_086475). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC149271. LOC157623 (Accession XM\_088346) is another VGAM676 host target gene. LOC157623 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157623, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157623 BINDING SITE, designated SEQ ID:39617, to the nucleotide sequence of VGAM676 RNA, herein designated VGAM RNA, also designated SEQ ID:3387.

[27722] Another function of VGAM676 is therefore inhibition of LOC157623 (Accession XM\_088346). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157623. LOC203197 (Accession XM\_114645) is another VGAM676 host target gene. LOC203197 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203197, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203197 BINDING SITE, designated SEQ ID:43010, to the nucleotide sequence of VGAM676 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3387.

[27723] Another function of VGAM676 is therefore inhibition of LOC203197 (Accession XM\_114645). Accordingly, utilities of VGAM676 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203197. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 677 (VGAM677) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27724] VGAM677 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM677 was detected is described hereinabove with reference to Figs. 1–8.

[27725] VGAM677 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM677 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27726] VGAM677 gene encodes a VGAM677 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM677 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM677 precursor RNA is designated SEQ ID:663, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:663 is located at position 4047 relative to the genome of Human Coronavirus 229E.

[27727] VGAM677 precursor RNA folds onto itself, forming VGAM677 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27728] An enzyme complex designated DICER COMPLEX, `dices` the VGAM677 folded precursor RNA into VGAM677 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM677 RNA is designated SEQ ID:3388, and is provided hereinbelow with reference to the sequence listing part.

[27729] VGAM677 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM677 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM677 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27730] VGAM677 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM677 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM677 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM677 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM677 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27731] The complementary binding of VGAM677 RNA, herein designated VGAM RNA, to host target binding sites on VGAM677 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM677 host target RNA into VGAM677 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27732] It is appreciated that VGAM677 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM677 host target genes. The mRNA of

each one of this plurality of VGAM677 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM677 RNA, herein designated VGAM RNA, and which when bound by VGAM677 RNA causes inhibition of translation of respective one or more VGAM677 host target proteins.

[27733] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM677 gene, herein designated VGAM GENE, on one or more VGAM677 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[27734] It is yet further appreciated that a function of VGAM677 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM677 correlate with, and may be deduced from, the identity of the host target genes which VGAM677 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27735] Nucleotide sequences of the VGAM677 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM677 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM677 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM677 are further described hereinbelow with reference to Table 1.

[27736] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM677 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM677 RNA, herein desig-



nated VGAM RNA, are described hereinbelow with reference to Table 2.

[27737] As mentioned hereinabove with reference to Fig. 1, a function of VGAM677 gene, herein designated VGAM is inhibition of expression of VGAM677 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM677 correlate with, and may be deduced from, the identity of the target genes which VGAM677 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27738] Adducin 1 (alpha) (ADD1, Accession NM\_014189) is a VGAM677 host target gene. ADD1 BINDING SITE1 and ADD1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ADD1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADD1 BINDING SITE1 and ADD1 BINDING SITE2, designated SEQ ID:15469 and SEQ ID:15473 respectively, to the nucleotide sequence of VGAM677 RNA, herein designated VGAM RNA, also designated SEQ ID:3388.

[27739] A function of VGAM677 is therefore inhibition of Adducin

1 (alpha) (ADD1, Accession NM\_014189), a gene which membrane-cytoskeleton- protein that promotes the assembly of the spectrin-actin network. Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADD1. The function of ADD1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM474. FXYD Domain Containing Ion Transport Regulator 6 (FXYD6, Accession NM\_022003) is another VGAM677 host target gene. FXYD6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FXYD6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FXYD6 BINDING SITE, designated SEQ ID:22551, to the nucleotide sequence of VGAM677 RNA, herein designated VGAM RNA, also designated SEQ ID:3388.

[27740] Another function of VGAM677 is therefore inhibition of FXYD Domain Containing Ion Transport Regulator 6 (FXYD6, Accession NM\_022003). Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FXVD6. Hepatocyte Growth Factor (hepatopoietin A; scatter factor) (HGF, Accession XM\_168542) is another VGAM677 host target gene. HGF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HGF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HGF BINDING SITE, designated SEQ ID:45229, to the nucleotide sequence of VGAM677 RNA, herein designated VGAM RNA, also designated SEQ ID:3388.

[27741] Another function of VGAM677 is therefore inhibition of Hepatocyte Growth Factor (hepatopoietin A; scatter factor) (HGF, Accession XM\_168542), a gene which may be required for normal embryonic development; strongly similar to murine Hgf, has kringle domains. Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HGF. The function of HGF and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM174. Transient Receptor Potential Cation Channel,

Subfamily V, Member 1 (TRPV1, Accession NM\_080706) is another VGAM677 host target gene. TRPV1 BINDING SITE1 through TRPV1 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TRPV1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPV1 BINDING SITE1 through TRPV1 BINDING SITE4, designated SEQ ID:28011, SEQ ID:27995, SEQ ID:28003 and SEQ ID:20815 respectively, to the nucleotide sequence of VGAM677 RNA, herein designated VGAM RNA, also designated SEQ ID:3388.

[27742] Another function of VGAM677 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily V, Member 1 (TRPV1, Accession NM\_080706), a gene which functions as a receptor for capsaicin. Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPV1. The function of TRPV1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM146.KIAA0240 (Accession XM\_166479) is another VGAM677 host target gene. KIAA0240 BINDING SITE is

HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0240, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0240 BINDING SITE, designated SEQ ID:44407, to the nucleotide sequence of VGAM677 RNA, herein designated VGAM RNA, also designated SEQ ID:3388.

[27743] Another function of VGAM677 is therefore inhibition of KIAA0240 (Accession XM\_166479). Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0240. Phosphodiesterase 11A (PDE11A, Accession NM\_016953) is another VGAM677 host target gene. PDE11A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PDE11A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDE11A BINDING SITE, designated SEQ ID:18868, to the nucleotide sequence of VGAM677 RNA, herein designated VGAM RNA, also designated SEQ ID:3388.

[27744] Another function of VGAM677 is therefore inhibition of Phosphodiesterase 11A (PDE11A, Accession NM\_016953). Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDE11A. LOC146268 (Accession XM\_085397) is another VGAM677 host target gene. LOC146268 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146268 BINDING SITE, designated SEQ ID:38125, to the nucleotide sequence of VGAM677 RNA, herein designated VGAM RNA, also designated SEQ ID:3388.

[27745] Another function of VGAM677 is therefore inhibition of LOC146268 (Accession XM\_085397). Accordingly, utilities of VGAM677 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146268. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 678 (VGAM678) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27746] VGAM678 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM678 was detected is described hereinabove with reference to Figs. 1–8.

[27747] VGAM678 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM678 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27748] VGAM678 gene encodes a VGAM678 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM678 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM678 precursor RNA is designated SEQ ID:664, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:664 is located at position 16921 relative to the genome of Human Coronavirus 229E.

[27749] VGAM678 precursor RNA folds onto itself, forming

VGAM678 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27750] An enzyme complex designated DICER COMPLEX, `dices` the VGAM678 folded precursor RNA into VGAM678 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM678 RNA is designated SEQ ID:3389, and is provided hereinbelow with reference to the sequence listing part.

[27751] VGAM678 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM678 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM678 host target RNA comprises



three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27752] VGAM678 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM678 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM678 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM678 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM678 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27753] The complementary binding of VGAM678 RNA, herein designated VGAM RNA, to host target binding sites on VGAM678 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM678 host target RNA into VGAM678 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27754] It is appreciated that VGAM678 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM678 host target genes. The mRNA of each one of this plurality of VGAM678 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM678 RNA, herein designated VGAM RNA, and which when bound by VGAM678 RNA causes inhibition of translation of respective one or more VGAM678 host target proteins.

[27755] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM678 gene, herein designated VGAM GENE, on one or more VGAM678 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27756] It is yet further appreciated that a function of VGAM678 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM678 correlate with, and may be deduced from, the identity of the host target genes which VGAM678 binds and inhibits,

and the function of these host target genes, as elaborated hereinbelow.

[27757] Nucleotide sequences of the VGAM678 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM678 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM678 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM678 are further described hereinbelow with reference to Table 1.

[27758] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM678 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM678 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27759] As mentioned hereinabove with reference to Fig. 1, a function of VGAM678 gene, herein designated VGAM is inhibition of expression of VGAM678 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM678 correlate with, and may be deduced from, the identity of the target genes which VGAM678 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[27760] Fibroblast Growth Factor 7 (keratinocyte growth factor) (FGF7, Accession NM\_002009) is a VGAM678 host target gene. FGF7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FGF7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF7 BINDING SITE, designated SEQ ID:7747, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27761] A function of VGAM678 is therefore inhibition of Fibroblast Growth Factor 7 (keratinocyte growth factor) (FGF7, Accession NM\_002009), a gene which growth factor active on keratinocytes. Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF7. The function of FGF7 has been established by previous studies. Rubin et al. (1989) identified a growth factor specific for epithelial cells in conditioned medium of a human embryonic lung fibroblast cell line. Because of its predominant activity in keratinocytes, it was referred to as keratinocyte growth factor. KGF was found to consist of a single polypeptide

chain of about 28 kD. It was a potent mitogen for epithelial cells but lacked mitogenic activity on either fibroblasts or endothelial cells. Microsequencing showed an amino-terminal sequence containing no significant homology to any known protein. The release of this growth factor by human embryonic fibroblasts raised the possibility that KGF may play a role in mesenchymal stimulation of normal epithelial cell proliferation. In an addendum, Rubin et al. (1989) noted that by use of all the nucleotide probes based on the N-terminal sequence reported in their paper, they had isolated clones encoding KGF and had found significant structural homology between KGF and the other 5 known members of the fibroblast growth factor (FGF) family. Werner et al. (1994) assessed the function of KGF in normal and wounded skin by expression of a dominant-negative KGF receptor (OMIM Ref. No. 176943) in basal keratinocytes. The skin of transgenic mice was characterized by epidermal atrophy, abnormalities in the hair follicles, and dermal hyperthickening. Upon skin injury, inhibition of KGF receptor signaling reduced the proliferation rate of epidermal keratinocytes at the wound edge, resulting in substantially delayed reepithelialization of the wound. Using a cosmid probe encoding KGF exon 1 for

fluorescence in situ hybridization, Zimonjic et al. (1997) assigned the KGF7 gene to 15q15–q21.1. In addition, copies of KGF–like sequences hybridizing only with a cos–mid probe encoding exons 2 and 3 were localized to dispersed sites on chromosome 2q21, 9p11, 9q12–q13, 18p11, 18q11, 21q11, and 21q21.1. The distribution of KGF–like sequences suggested a role for alphoid DNA in their amplification and dispersion. In chimpanzee, KGF–like sequences were observed at 5 chromosomal sites, which were each homologous to sites in human, while in gorilla a subset of 4 of these homologous sites was identified. In orangutan 2 sites were identified, while gibbon exhibited only a single site. The chromosomal localization of KGF sequences in human and great ape genomes indicated that amplification and dispersion occurred in multiple discrete steps, with initial KGF gene duplication and dispersion occurring in multiple discrete steps, with initial KGF gene duplication and dispersion taking place in gibbon and involving loci corresponding to human chromosomes 15 and 21. The findings of Zimonjic et al. (1997) supported the concept of a closer evolutionary relationship of human with chimpanzee and with primates and a possible selective pressure for KGF dispersion during the

evolution of higher primates.

[27762] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27763] Rubin, J. S.; Osada, H.; Finch, P. W.; Taylor, W. G.; Rudikoff, S.; Aaronson, S. A. : Purification and characterization of a newly identified growth factor specific for epithelial cells. Proc. Nat. Acad. Sci. 86: 802–806, 1989. ; and

[27764] Werner, S.; Smola, H.; Liao, X.; Longaker, M. T.; Krieg, T.; Hofschneider, P. H.; Williams, L. T. : The function of KGF in morphogenesis of epithelium and reepithelialization of wounds.

[27765] Further studies establishing the function and utilities of FGF7 are found in John Hopkins OMIM database record ID 148180, and in cited publications numbered 11377–11381 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Integrin, Alpha 1 (ITGA1, Accession XM\_032902) is another VGAM678 host target gene. ITGA1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ITGA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND–



ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGA1 BINDING SITE, designated SEQ ID:31792, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27766] Another function of VGAM678 is therefore inhibition of Integrin, Alpha 1 (ITGA1, Accession XM\_032902). Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGA1. Chromosome 20 Open Reading Frame 64 (C20orf64, Accession NM\_033550) is another VGAM678 host target gene. C20orf64 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf64, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf64 BINDING SITE, designated SEQ ID:27309, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27767] Another function of VGAM678 is therefore inhibition of Chromosome 20 Open Reading Frame 64 (C20orf64, Accession NM\_033550). Accordingly, utilities of VGAM678

include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf64. Sialyltransferase 8D (alpha-2, 8-polysialyltransferase) (SIAT8D, Accession NM\_005668) is another VGAM678 host target gene. SIAT8D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIAT8D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIAT8D BINDING SITE, designated SEQ ID:12222, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27768] Another function of VGAM678 is therefore inhibition of Sialyltransferase 8D (alpha-2, 8-polysialyltransferase) (SIAT8D, Accession NM\_005668). Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIAT8D. SNIP1 (Accession NM\_024700) is another VGAM678 host target gene. SNIP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SNIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of SNIP1 BINDING SITE, designated SEQ ID:24010, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27769] Another function of VGAM678 is therefore inhibition of SNIP1 (Accession NM\_024700). Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNIP1. LOC120448 (Accession XM\_062032) is another VGAM678 host target gene. LOC120448 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC120448, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120448 BINDING SITE, designated SEQ ID:37221, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27770] Another function of VGAM678 is therefore inhibition of LOC120448 (Accession XM\_062032). Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC120448. LOC145216 (Accession XM\_096730) is another VGAM678 host target gene. LOC145216 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145216, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145216 BINDING SITE, designated SEQ ID:40504, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27771] Another function of VGAM678 is therefore inhibition of LOC145216 (Accession XM\_096730). Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145216. LOC154743 (Accession XM\_088029) is another VGAM678 host target gene. LOC154743 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154743, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154743 BINDING SITE, designated SEQ ID:39481, to the nucleotide sequence of VGAM678 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3389.

[27772] Another function of VGAM678 is therefore inhibition of LOC154743 (Accession XM\_088029). Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154743. LOC196812 (Accession XM\_116868) is another VGAM678 host target gene. LOC196812 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196812, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196812 BINDING SITE, designated SEQ ID:43134, to the nucleotide sequence of VGAM678 RNA, herein designated VGAM RNA, also designated SEQ ID:3389.

[27773] Another function of VGAM678 is therefore inhibition of LOC196812 (Accession XM\_116868). Accordingly, utilities of VGAM678 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196812. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 679 (VGAM679) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27774] VGAM679 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM679 was detected is described hereinabove with reference to Figs. 1–8.

[27775] VGAM679 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM679 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27776] VGAM679 gene encodes a VGAM679 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM679 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM679 precursor RNA is designated SEQ ID:665, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:665 is located at position 1569 relative to the genome of Human Coronavirus 229E.

[27777] VGAM679 precursor RNA folds onto itself, forming

VGAM679 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27778] An enzyme complex designated DICER COMPLEX, `dices` the VGAM679 folded precursor RNA into VGAM679 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM679 RNA is designated SEQ ID:3390, and is provided hereinbelow with reference to the sequence listing part.

[27779] VGAM679 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM679 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM679 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27780] VGAM679 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM679 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM679 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM679 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM679 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example



only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27781] The complementary binding of VGAM679 RNA, herein designated VGAM RNA, to host target binding sites on VGAM679 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM679 host target RNA into VGAM679 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27782] It is appreciated that VGAM679 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM679 host target genes. The mRNA of each one of this plurality of VGAM679 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM679 RNA, herein designated VGAM RNA, and which when bound by VGAM679 RNA causes inhibition of translation of respective one or more VGAM679 host target proteins.

[27783] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM679 gene, herein designated VGAM GENE, on one or more VGAM679 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27784] It is yet further appreciated that a function of VGAM679 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM679 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM679 correlate with, and may be deduced from, the identity of the host target genes which VGAM679 binds and inhibits,

and the function of these host target genes, as elaborated hereinbelow.

[27785] Nucleotide sequences of the VGAM679 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM679 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM679 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM679 are further described hereinbelow with reference to Table 1.

[27786] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM679 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM679 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27787] As mentioned hereinabove with reference to Fig. 1, a function of VGAM679 gene, herein designated VGAM is inhibition of expression of VGAM679 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM679 correlate with, and may be deduced from, the identity of the target genes which VGAM679 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[27788] V-abl Abelson Murine Leukemia Viral Oncogene Homolog 1 (ABL1, Accession NM\_005157) is a VGAM679 host target gene. ABL1 BINDING SITE1 and ABL1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABL1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABL1 BINDING SITE1 and ABL1 BINDING SITE2, designated SEQ ID:11635 and SEQ ID:14224 respectively, to the nucleotide sequence of VGAM679 RNA, herein designated VGAM RNA, also designated SEQ ID:3390.

[27789] A function of VGAM679 is therefore inhibition of V-abl Abelson Murine Leukemia Viral Oncogene Homolog 1 (ABL1, Accession NM\_005157). Accordingly, utilities of VGAM679 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABL1. Parkinson Disease (autosomal recessive, juvenile) 2, Parkin (PARK2, Accession NM\_013988) is another VGAM679 host target gene. PARK2 BINDING SITE1 through PARK2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PARK2, corre-

sponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PARK2 BINDING SITE1 through PARK2 BINDING SITE3, designated SEQ ID:15155, SEQ ID:10901 and SEQ ID:15148 respectively, to the nucleotide sequence of VGAM679 RNA, herein designated VGAM RNA, also designated SEQ ID:3390.

[27790] Another function of VGAM679 is therefore inhibition of Parkinson Disease (autosomal recessive, juvenile) 2, Parkin (PARK2, Accession NM\_013988). Accordingly, utilities of VGAM679 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PARK2. SAC2 Suppressor of Actin Mutations 2-like (yeast) (SACM2L, Accession NM\_080564) is another VGAM679 host target gene. SACM2L BINDING SITE1 and SACM2L BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SACM2L, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SACM2L BINDING SITE1 and SACM2L BINDING SITE2, designated SEQ ID:27885 and SEQ ID:21841 respectively, to

the nucleotide sequence of VGAM679 RNA, herein designated VGAM RNA, also designated SEQ ID:3390.

[27791] Another function of VGAM679 is therefore inhibition of SAC2 Suppressor of Actin Mutations 2-like (yeast) (SACM2L, Accession NM\_080564). Accordingly, utilities of VGAM679 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SACM2L. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 680 (VGAM680) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27792] VGAM680 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM680 was detected is described hereinabove with reference to Figs. 1–8.

[27793] VGAM680 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM680 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27794] VGAM680 gene encodes a VGAM680 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM680 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM680 precursor RNA is designated SEQ ID:666, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:666 is located at position 14292 relative to the genome of Human Coronavirus 229E.

[27795] VGAM680 precursor RNA folds onto itself, forming VGAM680 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27796] An enzyme complex designated DICER COMPLEX, `dices` the VGAM680 folded precursor RNA into VGAM680 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM680 RNA is designated SEQ ID:3391, and is provided hereinbelow with reference to the sequence listing part.

[27797] VGAM680 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM680 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM680 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27798] VGAM680 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM680 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM680 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding



sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM680 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM680 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27799] The complementary binding of VGAM680 RNA, herein designated VGAM RNA, to host target binding sites on VGAM680 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM680 host target RNA into VGAM680 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27800] It is appreciated that VGAM680 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM680 host target genes. The mRNA of each one of this plurality of VGAM680 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM680 RNA, herein designated VGAM RNA, and which when bound by VGAM680 RNA causes inhibition of translation of respective one or more VGAM680 host target proteins.

[27801] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM680 gene, herein designated VGAM GENE, on one or more VGAM680 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[27802] It is yet further appreciated that a function of VGAM680 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM680 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM680 correlate with, and may be deduced from, the identity of the host target genes which VGAM680 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27803] Nucleotide sequences of the VGAM680 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM680 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM680 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM680 are further described hereinbelow with reference to Table 1.

[27804] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM680 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM680 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27805] As mentioned hereinabove with reference to Fig. 1, a function of VGAM680 gene, herein designated VGAM is inhibition of expression of VGAM680 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM680 correlate with, and may be deduced from, the identity of the target genes which VGAM680 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27806] ATPase, H<sup>+</sup> Transporting, Lysosomal 13kDa, V1 Subunit G Isoform 2 (ATP6V1G2, Accession NM\_130463) is a VGAM680 host target gene. ATP6V1G2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ATP6V1G2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP6V1G2 BINDING SITE, designated SEQ ID:28224, to the nucleotide sequence of VGAM680 RNA, herein designated VGAM RNA, also designated SEQ ID:3391.

[27807] A function of VGAM680 is therefore inhibition of ATPase,

H<sup>+</sup> Transporting, Lysosomal 13kDa, V1 Subunit G Isoform 2 (ATP6V1G2, Accession NM\_130463). Accordingly, utilities of VGAM680 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP6V1G2. Inositol 1,4,5-triphosphate Receptor, Type 2 (ITPR2, Accession NM\_002223) is another VGAM680 host target gene. ITPR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITPR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITPR2 BINDING SITE, designated SEQ ID:7988, to the nucleotide sequence of VGAM680 RNA, herein designated VGAM RNA, also designated SEQ ID:3391.

[27808] Another function of VGAM680 is therefore inhibition of Inositol 1,4,5-triphosphate Receptor, Type 2 (ITPR2, Accession NM\_002223). Accordingly, utilities of VGAM680 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITPR2. PSA (Accession NM\_021154) is another VGAM680 host target gene. PSA BINDING SITE1 and PSA BINDING SITE2 are HOST TARGET binding sites found in untranslated regions

of mRNA encoded by PSA, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PSA BINDING SITE1 and PSA BINDING SITE2, designated SEQ ID:22128 and SEQ ID:27737 respectively, to the nucleotide sequence of VGAM680 RNA, herein designated VGAM RNA, also designated SEQ ID:3391.

[27809] Another function of VGAM680 is therefore inhibition of PSA (Accession NM\_021154), a gene which is puromycin-sensitive aminopeptidase and has metallopeptidase activity. Accordingly, utilities of VGAM680 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PSA. The function of PSA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM65.LOC146455 (Accession XM\_085471) is another VGAM680 host target gene.

LOC146455 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146455, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of LOC146455 BINDING SITE, designated SEQ ID:38155, to the nucleotide sequence of VGAM680 RNA, herein designated VGAM RNA, also designated SEQ ID:3391.

[27810] Another function of VGAM680 is therefore inhibition of LOC146455 (Accession XM\_085471). Accordingly, utilities of VGAM680 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146455. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 681 (VGAM681) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27811] VGAM681 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM681 was detected is described hereinabove with reference to Figs. 1–8.

[27812] VGAM681 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM681 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in

the human genome.

[27813] VGAM681 gene encodes a VGAM681 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM681 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM681 precursor RNA is designated SEQ ID:667, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:667 is located at position 9140 relative to the genome of Human Coronavirus 229E.

[27814] VGAM681 precursor RNA folds onto itself, forming VGAM681 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27815] An enzyme complex designated DICER COMPLEX, `dices` the VGAM681 folded precursor RNA into VGAM681 RNA, herein designated VGAM RNA, a single stranded ~22 nt



long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM681 RNA is designated SEQ ID:3392, and is provided hereinbelow with reference to the sequence listing part.

[27816] VGAM681 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM681 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM681 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27817] VGAM681 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM681 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM681 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM681 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM681 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27818] The complementary binding of VGAM681 RNA, herein designated VGAM RNA, to host target binding sites on VGAM681 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM681 host target RNA into VGAM681 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27819] It is appreciated that VGAM681 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM681 host target genes. The mRNA of each one of this plurality of VGAM681 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM681 RNA, herein designated VGAM RNA, and which when bound by VGAM681 RNA causes inhibition of translation of respective one or more VGAM681 host target proteins.

[27820] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM681 gene, herein designated VGAM GENE, on one or more VGAM681 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27821] It is yet further appreciated that a function of VGAM681 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM681 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM681 correlate with, and may be deduced from, the identity of the host target genes which VGAM681 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27822] Nucleotide sequences of the VGAM681 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM681 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM681 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM681 are further described hereinbelow with reference to Table 1.

[27823] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM681 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM681 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27824] As mentioned hereinabove with reference to Fig. 1, a function of VGAM681 gene, herein designated VGAM is inhibition of expression of VGAM681 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM681 correlate with, and may be deduced from, the identity of the target genes which VGAM681 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27825] NKX3A (Accession NM\_006167) is a VGAM681 host target gene. NKX3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NKX3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NKX3A BINDING SITE, designated SEQ ID:12830, to the nucleotide sequence of VGAM681 RNA, herein designated VGAM RNA, also designated SEQ ID:3392.

[27826] A function of VGAM681 is therefore inhibition of NKX3A (Accession NM\_006167), a gene which may regulate gene expression and control cell differentiation. Accordingly, utilities of VGAM681 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NKX3A. The function of NKX3A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM481. Ankyrin Repeat and SOCS Box-containing 13 (ASB13, Accession NM\_024701) is another VGAM681 host target gene. ASB13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ASB13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASB13 BINDING SITE, designated SEQ ID:24011, to the nucleotide sequence of VGAM681 RNA, herein designated VGAM RNA, also designated SEQ ID:3392.

[27827] Another function of VGAM681 is therefore inhibition of Ankyrin Repeat and SOCS Box-containing 13 (ASB13, Accession NM\_024701). Accordingly, utilities of VGAM681 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with ASB13. FLJ20273 (Accession NM\_019027) is another VGAM681 host target gene. FLJ20273 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20273 BINDING SITE, designated SEQ ID:21113, to the nucleotide sequence of VGAM681 RNA, herein designated VGAM RNA, also designated SEQ ID:3392.

[27828] Another function of VGAM681 is therefore inhibition of FLJ20273 (Accession NM\_019027). Accordingly, utilities of VGAM681 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20273. KIAA1336 (Accession XM\_051306) is another VGAM681 host target gene. KIAA1336 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1336, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1336 BINDING SITE, designated SEQ ID:35799, to the nucleotide sequence of

VGAM681 RNA, herein designated VGAM RNA, also designated SEQ ID:3392.

[27829] Another function of VGAM681 is therefore inhibition of KIAA1336 (Accession XM\_051306). Accordingly, utilities of VGAM681 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1336. LOC161742 (Accession XM\_091095) is another VGAM681 host target gene. LOC161742 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC161742, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161742 BINDING SITE, designated SEQ ID:40025, to the nucleotide sequence of VGAM681 RNA, herein designated VGAM RNA, also designated SEQ ID:3392.

[27830] Another function of VGAM681 is therefore inhibition of LOC161742 (Accession XM\_091095). Accordingly, utilities of VGAM681 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161742. LOC255919 (Accession XM\_170794) is another VGAM681 host target gene. LOC255919 BINDING SITE is HOST TARGET binding site found in the 3' un-



translated region of mRNA encoded by LOC255919, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255919 BINDING SITE, designated SEQ ID:45554, to the nucleotide sequence of VGAM681 RNA, herein designated VGAM RNA, also designated SEQ ID:3392.

[27831] Another function of VGAM681 is therefore inhibition of LOC255919 (Accession XM\_170794). Accordingly, utilities of VGAM681 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255919. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 682 (VGAM682) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27832] VGAM682 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM682 was detected is described hereinabove with reference to Figs. 1–8.

[27833] VGAM682 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Human Coronavirus 229E. VGAM682 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27834] VGAM682 gene encodes a VGAM682 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM682 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM682 precursor RNA is designated SEQ ID:668, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:668 is located at position 7304 relative to the genome of Human Coronavirus 229E.

[27835] VGAM682 precursor RNA folds onto itself, forming VGAM682 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27836] An enzyme complex designated DICER COMPLEX, `dices` the VGAM682 folded precursor RNA into VGAM682 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 56%) nucleotide sequence of VGAM682 RNA is designated SEQ ID:3393, and is provided hereinbelow with reference to the sequence listing part.

[27837] VGAM682 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM682 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM682 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27838] VGAM682 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM682 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM682 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM682 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM682 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27839] The complementary binding of VGAM682 RNA, herein designated VGAM RNA, to host target binding sites on VGAM682 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM682 host tar-

get RNA into VGAM682 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27840] It is appreciated that VGAM682 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM682 host target genes. The mRNA of each one of this plurality of VGAM682 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM682 RNA, herein designated VGAM RNA, and which when bound by VGAM682 RNA causes inhibition of translation of respective one or more VGAM682 host target proteins.

[27841] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM682 gene, herein designated VGAM GENE, on one or more VGAM682 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27842] It is yet further appreciated that a function of VGAM682 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM682 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM682 correlate with, and may be deduced from, the identity of the host target genes which VGAM682 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27843] Nucleotide sequences of the VGAM682 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM682 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM682 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM682 are further

described hereinbelow with reference to Table 1.

[27844] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM682 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM682 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27845] As mentioned hereinabove with reference to Fig. 1, a function of VGAM682 gene, herein designated VGAM is inhibition of expression of VGAM682 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM682 correlate with, and may be deduced from, the identity of the target genes which VGAM682 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27846] Myeloid/lymphoid Or Mixed-lineage Leukemia (trithorax homolog, Drosophila); Translocated To, 2 (MLLT2, Accession NM\_005935) is a VGAM682 host target gene. MLLT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MLLT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of MLLT2 BINDING SITE, designated SEQ ID:12570, to the nucleotide sequence of VGAM682 RNA, herein designated VGAM RNA, also designated SEQ ID:3393.

[27847] A function of VGAM682 is therefore inhibition of Myeloid/lymphoid Or Mixed-lineage Leukemia (trithorax homolog, Drosophila); Translocated To, 2 (MLLT2, Accession NM\_005935), a gene which is a Putative transcription factor. Accordingly, utilities of VGAM682 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MLLT2. The function of MLLT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM57. Protein S (alpha) (PROS1, Accession XM\_113400) is another VGAM682 host target gene. PROS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PROS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PROS1 BINDING SITE, designated SEQ ID:42255, to the nucleotide sequence of VGAM682 RNA, herein designated VGAM RNA, also desig-



nated SEQ ID:3393.

[27848] Another function of VGAM682 is therefore inhibition of Protein S (alpha) (PROS1, Accession XM\_113400). Accordingly, utilities of VGAM682 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PROS1. Thiopurine S-methyltransferase (TPMT, Accession NM\_000367) is another VGAM682 host target gene. TPMT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TPMT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TPMT BINDING SITE, designated SEQ ID:5940, to the nucleotide sequence of VGAM682 RNA, herein designated VGAM RNA, also designated SEQ ID:3393.

[27849] Another function of VGAM682 is therefore inhibition of Thiopurine S-methyltransferase (TPMT, Accession NM\_000367), a gene which catalyzes the s-methylation of thiopurine drugs such as 6-mercaptopurine. Accordingly, utilities of VGAM682 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TPMT. The function of TPMT has been established by previous studies. Thiopurine S-methyltransferase (TPMT;

S-adenosyl-L-methionine:thiopurine S-methyltransferase; EC 2.1.1.67) catalyzes thiopurine S-methylation, an important metabolic pathway for drugs such as 6-mercaptopurine. Weinshilboum and Sladek (1980) found trimodality for level of red cell TPMT among 298 randomly selected subjects: 88.6% had high enzyme activity; 11.1% had intermediate activity and 0.3% had undetectable activity. This distribution conforms to Hardy-Weinberg expectations for a pair of autosomal codominant alleles for low and high activity, TPMT-L and TPMT-H, with frequencies of 0.059 and 0.941, respectively. Segregation in families ascertained through probands with undetectable activity was consistent with this hypothesis. This genetic polymorphism may be an important factor in individual variations in sensitivity to thiopurines.

6-Mercaptopurine (6-MP) can be inactivated by S-methylation, which is catalyzed by thiopurine methyltransferase. An alternative metabolic route leads to the formation of cytotoxic 6-thioguanine nucleotides (6-TGN). Lennard et al. (1990) investigated whether these 2 pathways compete to affect the therapeutic response to 6-MP, by measuring 6-TGN concentrations and TPMT enzymatic activity in red cells of 95 children on long-term

6-MP therapy for acute lymphoblastic leukemia (ALL). Red cell TPMT activities were also measured in 130 control children and 104 long-term survivors of ALL no longer on treatment. In the children on 6-MP, red cell 6-TGN correlated negatively with red cell TPMT activity. Children with 6-TGN concentrations below the group mean had higher TPMT activities and a higher subsequent relapse rate. Fifty of the 104 long-term survivors had been treated with low-dose protocols; this subgroup contained an excess of children with lower TPMT activities. The results indicated that genetically determined TPMT activity may be an important regulator of the cytotoxic effect of 6-MP, an effect which in turn may be important in influencing the outcome of therapy for childhood ALL. Klemetsdal et al. (1993) found in a group of healthy subjects that red blood cell TPMT activity was 8.3% higher in male subjects than in female subjects. Alves et al. (1999) applied a PCR-SSCP method for TPMT-specific detection which introduces a substantial technical simplification, avoiding the use of restriction enzyme treatment after PCR amplification. Additionally, the method allowed the simultaneous detection of a 474T-C transition, a frequent silent mutation in the non-Portuguese population (TPMT\*1S = 0.215). In a sam-

ple of 310 unrelated Northern Portuguese individuals, 15 were found to be heterozygous for the TPMT\*3A allele (187680.0002) which is associated with TPMT enzymatic deficiency; the corresponding gene frequency estimate was 0.024. In an attempt to evaluate the relationship between the molecular TPMT genotype and reaction to treatments involving thiopurine drugs, Alves et al. (1999) analyzed a sample of 24 children who received curative therapy of acute lymphoblastic leukemia. Four of them were shown to be heterozygous for the TPMT\*3A allele. An examination of their clinical histories showed that all 4 patients exhibited signs of severe hepatic toxicity during treatment. McLeod et al. (1999) studied the frequency of common TPMT variant alleles in 101 Kenyan individuals and 199 Caucasians. The frequency of mutant alleles was similar between the Caucasian (10.1%) and Kenyan (10.9%) populations; however, all mutant alleles in the Kenyan population were TPMT\*3C (187680.0005) compared with 4.8% in Caucasians. In contrast, TPMT\*3A (187680.0002) was the most common mutant allele in the Caucasian individuals.

[27850] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [27851] Alves, S.; Prata, M.-J.; Ferreira, F.; Amorim, A. : Thiopurine methyltransferase pharmacogenetics: alternative molecular diagnosis and preliminary data from Northern Portugal. *Pharmacogenetics* 9: 257–261, 1999. ; and
- [27852] Ameyaw, M.-M.; Collie-Duguid, E. S. R.; Powrie, R. H.; Ofori-Adjei, D.; McLeod, H. L. : Thiopurine methyltransferase alleles in British and Ghanaian populations. *Hum. Molec. Genet.* 8: 3.
- [27853] Further studies establishing the function and utilities of TPMT are found in John Hopkins OMIM database record ID 187680, and in cited publications numbered 540–556 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZP566J091 (Accession NM\_030915) is another VGAM682 host target gene. DKFZP566J091 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP566J091, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566J091 BINDING SITE, designated SEQ ID:25186, to the nucleotide sequence of VGAM682 RNA, herein designated VGAM RNA,

also designated SEQ ID:3393.

[27854] Another function of VGAM682 is therefore inhibition of DKFZP566J091 (Accession NM\_030915). Accordingly, utilities of VGAM682 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566J091. ERAP140 (Accession XM\_059748) is another VGAM682 host target gene. ERAP140 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ERAP140, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ERAP140 BINDING SITE, designated SEQ ID:37082, to the nucleotide sequence of VGAM682 RNA, herein designated VGAM RNA, also designated SEQ ID:3393.

[27855] Another function of VGAM682 is therefore inhibition of ERAP140 (Accession XM\_059748). Accordingly, utilities of VGAM682 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ERAP140. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 683 (VGAM683) viral gene, which modulates expression of

respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27856] VGAM683 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM683 was detected is described hereinabove with reference to Figs. 1–8.

[27857] VGAM683 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM683 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27858] VGAM683 gene encodes a VGAM683 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM683 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM683 precursor RNA is designated SEQ ID:669, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:669 is located at position 19339 relative to the genome of Human Coronavirus 229E.

[27859] VGAM683 precursor RNA folds onto itself, forming VGAM683 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[27860] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM683 folded precursor RNA into VGAM683 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 45%) nucleotide se-  
quence of VGAM683 RNA is designated SEQ ID:3394, and  
is provided hereinbelow with reference to the sequence  
listing part.

[27861] VGAM683 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM683 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM683 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding



gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27862] VGAM683 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM683 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM683 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM683 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM683 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27863] The complementary binding of VGAM683 RNA, herein designated VGAM RNA, to host target binding sites on VGAM683 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM683 host target RNA into VGAM683 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27864] It is appreciated that VGAM683 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM683 host target genes. The mRNA of each one of this plurality of VGAM683 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM683 RNA, herein designated VGAM RNA, and which when bound by VGAM683 RNA causes inhibition of translation of respective one or more VGAM683 host target proteins.

[27865] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM683 gene, herein designated VGAM GENE, on one or more VGAM683 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27866] It is yet further appreciated that a function of VGAM683 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM683 correlate with, and may be deduced from, the identity of the host target genes which VGAM683 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

[27867] Nucleotide sequences of the VGAM683 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM683 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM683 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM683 are further described hereinbelow with reference to Table 1.

[27868] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM683 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM683 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27869] As mentioned hereinabove with reference to Fig. 1, a function of VGAM683 gene, herein designated VGAM is inhibition of expression of VGAM683 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM683 correlate with, and may be deduced from, the identity of the target genes which VGAM683 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27870] Nuclear Factor I/A (NFIA, Accession XM\_046827) is a VGAM683 host target gene. NFIA BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NFIA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFIA BINDING SITE, designated SEQ ID:34838, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27871] A function of VGAM683 is therefore inhibition of Nuclear Factor I/A (NFIA, Accession XM\_046827). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NFIA. Solute Carrier Family 20 (phosphate transporter), Member 1 (SLC20A1, Accession XM\_002217) is another VGAM683 host target gene. SLC20A1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SLC20A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC20A1 BINDING SITE, designated SEQ ID:29872, to the

nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27872] Another function of VGAM683 is therefore inhibition of Solute Carrier Family 20 (phosphate transporter), Member 1 (SLC20A1, Accession XM\_002217), a gene which could be a sodium–phosphate symporter. Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC20A1. The function of SLC20A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM608.FLJ13782 (Accession NM\_024915) is another VGAM683 host target gene. FLJ13782 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13782, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13782 BINDING SITE, designated SEQ ID:24438, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27873] Another function of VGAM683 is therefore inhibition of

FLJ13782 (Accession NM\_024915). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13782. FLJ14054 (Accession NM\_024563) is another VGAM683 host target gene. FLJ14054 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14054, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14054 BINDING SITE, designated SEQ ID:23782, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27874] Another function of VGAM683 is therefore inhibition of FLJ14054 (Accession NM\_024563). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14054. GCN2 (Accession XM\_031612) is another VGAM683 host target gene. GCN2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GCN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of GCN2 BINDING SITE, designated SEQ ID:31445, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27875] Another function of VGAM683 is therefore inhibition of GCN2 (Accession XM\_031612). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GCN2. KIAA0570 (Accession NM\_014709) is another VGAM683 host target gene. KIAA0570 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0570, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0570 BINDING SITE, designated SEQ ID:16254, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27876] Another function of VGAM683 is therefore inhibition of KIAA0570 (Accession NM\_014709). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0570. TIP-1 (Accession NM\_014604) is another



VGAM683 host target gene. TIP-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIP-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIP-1 BINDING SITE, designated SEQ ID:15967, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27877] Another function of VGAM683 is therefore inhibition of TIP-1 (Accession NM\_014604). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIP-1. LOC152765 (Accession XM\_087519) is another VGAM683 host target gene. LOC152765 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152765, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152765 BINDING SITE, designated SEQ ID:39313, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27878] Another function of VGAM683 is therefore inhibition of LOC152765 (Accession XM\_087519). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152765. LOC163412 (Accession XM\_088868) is another VGAM683 host target gene. LOC163412 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163412, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163412 BINDING SITE, designated SEQ ID:39954, to the nucleotide sequence of VGAM683 RNA, herein designated VGAM RNA, also designated SEQ ID:3394.

[27879] Another function of VGAM683 is therefore inhibition of LOC163412 (Accession XM\_088868). Accordingly, utilities of VGAM683 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163412. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 684 (VGAM684) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[27880] VGAM684 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM684 was detected is described hereinabove with reference to Figs. 1–8.

[27881] VGAM684 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM684 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27882] VGAM684 gene encodes a VGAM684 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM684 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM684 precursor RNA is designated SEQ ID:670, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:670 is located at position 18943 relative to the genome of Human Coronavirus 229E.

[27883] VGAM684 precursor RNA folds onto itself, forming VGAM684 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[27884] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM684 folded precursor RNA into VGAM684 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 42%) nucleotide se-  
quence of VGAM684 RNA is designated SEQ ID:3395, and  
is provided hereinbelow with reference to the sequence  
listing part.

[27885] VGAM684 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM684 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM684 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27886] VGAM684 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM684 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM684 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM684 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM684 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27887] The complementary binding of VGAM684 RNA, herein designated VGAM RNA, to host target binding sites on VGAM684 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM684 host target RNA into VGAM684 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27888] It is appreciated that VGAM684 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM684 host target genes. The mRNA of each one of this plurality of VGAM684 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM684 RNA, herein designated VGAM RNA, and which when bound by VGAM684 RNA causes inhibition of translation of respective one or more VGAM684 host target proteins.

[27889] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM684 gene, herein designated VGAM GENE, on one or more VGAM684 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27890] It is yet further appreciated that a function of VGAM684 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM684 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM684 correlate with, and may be deduced from, the identity of the host target genes which VGAM684 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

[27891] Nucleotide sequences of the VGAM684 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM684 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM684 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM684 are further described hereinbelow with reference to Table 1.

[27892] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM684 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM684 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27893] As mentioned hereinabove with reference to Fig. 1, a function of VGAM684 gene, herein designated VGAM is inhibition of expression of VGAM684 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM684 correlate with, and may be deduced from, the identity of the target genes which VGAM684 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.



[27894] Guanine Nucleotide Binding Protein (G protein), Alpha 15 (Gq class) (GNA15, Accession XM\_009220) is a VGAM684 host target gene. GNA15 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GNA15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GNA15 BINDING SITE, designated SEQ ID:30106, to the nucleotide sequence of VGAM684 RNA, herein designated VGAM RNA, also designated SEQ ID:3395.

[27895] A function of VGAM684 is therefore inhibition of Guanine Nucleotide Binding Protein (G protein), Alpha 15 (Gq class) (GNA15, Accession XM\_009220). Accordingly, utilities of VGAM684 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNA15. FLJ10620 (Accession NM\_018157) is another VGAM684 host target gene. FLJ10620 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10620, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10620 BINDING SITE,

designated SEQ ID:19972, to the nucleotide sequence of VGAM684 RNA, herein designated VGAM RNA, also designated SEQ ID:3395.

[27896] Another function of VGAM684 is therefore inhibition of FLJ10620 (Accession NM\_018157). Accordingly, utilities of VGAM684 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10620. HCGIV.9 (Accession NM\_018985) is another VGAM684 host target gene. HCGIV.9 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HCGIV.9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCGIV.9 BINDING SITE, designated SEQ ID:21057, to the nucleotide sequence of VGAM684 RNA, herein designated VGAM RNA, also designated SEQ ID:3395.

[27897] Another function of VGAM684 is therefore inhibition of HCGIV.9 (Accession NM\_018985). Accordingly, utilities of VGAM684 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCGIV.9. TNF Receptor-associated Factor 3 (TRAF3, Accession XM\_007256) is another VGAM684 host target gene. TRAF3

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRAF3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRAF3 BINDING SITE, designated SEQ ID:30048, to the nucleotide sequence of VGAM684 RNA, herein designated VGAM RNA, also designated SEQ ID:3395.

[27898] Another function of VGAM684 is therefore inhibition of TNF Receptor-associated Factor 3 (TRAF3, Accession XM\_007256). Accordingly, utilities of VGAM684 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRAF3. LOC145255 (Accession XM\_096748) is another VGAM684 host target gene. LOC145255 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145255 BINDING SITE, designated SEQ ID:40527, to the nucleotide sequence of VGAM684 RNA, herein designated VGAM RNA, also designated SEQ ID:3395.

[27899] Another function of VGAM684 is therefore inhibition of LOC145255 (Accession XM\_096748). Accordingly, utilities of VGAM684 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145255. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 685 (VGAM685) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27900] VGAM685 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM685 was detected is described hereinabove with reference to Figs. 1–8.

[27901] VGAM685 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM685 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27902] VGAM685 gene encodes a VGAM685 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM685

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM685 precursor RNA is designated SEQ ID:671, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:671 is located at position 8018 relative to the genome of Human Coronavirus 229E.

[27903] VGAM685 precursor RNA folds onto itself, forming VGAM685 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27904] An enzyme complex designated DICER COMPLEX, `dices` the VGAM685 folded precursor RNA into VGAM685 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 45%) nucleotide sequence of VGAM685 RNA is designated SEQ ID:3396, and is provided hereinbelow with reference to the sequence listing part.

[27905] VGAM685 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM685 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM685 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[27906] VGAM685 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM685 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM685 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM685 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM685 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27907] The complementary binding of VGAM685 RNA, herein designated VGAM RNA, to host target binding sites on VGAM685 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM685 host target RNA into VGAM685 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27908] It is appreciated that VGAM685 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM685 host target genes. The mRNA of each one of this plurality of VGAM685 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM685 RNA, herein designated VGAM RNA, and which when bound by VGAM685 RNA causes inhibition of translation of respective one or more VGAM685 host target proteins.

[27909] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM685 gene, herein designated VGAM GENE, on one or more VGAM685 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).



[27910] It is yet further appreciated that a function of VGAM685 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM685 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM685 correlate with, and may be deduced from, the identity of the host target genes which VGAM685 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27911] Nucleotide sequences of the VGAM685 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM685 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM685 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM685 are further described hereinbelow with reference to Table 1.

[27912] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM685 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM685 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[27913] As mentioned hereinabove with reference to Fig. 1, a function of VGAM685 gene, herein designated VGAM is inhibition of expression of VGAM685 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM685 correlate with, and may be deduced from, the identity of the target genes which VGAM685 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27914] Potassium Inwardly-rectifying Channel, Subfamily J, Member 14 (KCNJ14, Accession NM\_013348) is a VGAM685 host target gene. KCNJ14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNJ14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNJ14 BINDING SITE, designated SEQ ID:14993, to the nucleotide sequence of VGAM685 RNA, herein designated VGAM RNA, also designated SEQ ID:3396.

[27915] A function of VGAM685 is therefore inhibition of Potassium Inwardly-rectifying Channel, Subfamily J, Member 14 (KCNJ14, Accession NM\_013348). Accordingly, utilities of

VGAM685 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNJ14. KIAA0431 (Accession NM\_015251) is another VGAM685 host target gene. KIAA0431 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0431, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0431 BINDING SITE, designated SEQ ID:17580, to the nucleotide sequence of VGAM685 RNA, herein designated VGAM RNA, also designated SEQ ID:3396.

[27916] Another function of VGAM685 is therefore inhibition of KIAA0431 (Accession NM\_015251). Accordingly, utilities of VGAM685 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0431. KIAA1371 (Accession XM\_114371) is another VGAM685 host target gene. KIAA1371 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1371, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1371 BINDING SITE, designated SEQ ID:42909, to the nucleotide sequence of VGAM685 RNA, herein designated VGAM RNA, also designated SEQ ID:3396.

[27917] Another function of VGAM685 is therefore inhibition of KIAA1371 (Accession XM\_114371). Accordingly, utilities of VGAM685 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1371. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 686 (VGAM686) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27918] VGAM686 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM686 was detected is described hereinabove with reference to Figs. 1–8.

[27919] VGAM686 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM686 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27920] VGAM686 gene encodes a VGAM686 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM686 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM686 precursor RNA is designated SEQ ID:672, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:672 is located at position 14152 relative to the genome of Human Coronavirus 229E.

[27921] VGAM686 precursor RNA folds onto itself, forming VGAM686 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27922] An enzyme complex designated DICER COMPLEX, `dices` the VGAM686 folded precursor RNA into VGAM686 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM686 RNA is designated SEQ ID:3397, and is provided hereinbelow with reference to the sequence listing part.

[27923] VGAM686 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM686 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM686 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27924] VGAM686 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM686 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM686 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM686 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM686 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27925] The complementary binding of VGAM686 RNA, herein designated VGAM RNA, to host target binding sites on VGAM686 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM686 host target RNA into VGAM686 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27926] It is appreciated that VGAM686 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM686 host target genes. The mRNA of each one of this plurality of VGAM686 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM686 RNA, herein designated VGAM RNA, and which when bound by VGAM686 RNA causes inhibition of translation of respective one or more VGAM686 host target proteins.

[27927] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM686 gene, herein designated VGAM GENE, on one or more VGAM686 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these



other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[27928] It is yet further appreciated that a function of VGAM686 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM686 correlate with, and may be deduced from, the identity of the host target genes which VGAM686 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27929] Nucleotide sequences of the VGAM686 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM686 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM686 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM686 are further described hereinbelow with reference to Table 1.

[27930] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM686 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM686 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27931] As mentioned hereinabove with reference to Fig. 1, a function of VGAM686 gene, herein designated VGAM is inhibition of expression of VGAM686 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM686 correlate with, and may be deduced from, the identity of the target genes which VGAM686 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27932] COX11 Homolog, Cytochrome C Oxidase Assembly Protein (yeast) (COX11, Accession NM\_004375) is a VGAM686 host target gene. COX11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COX11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COX11 BINDING SITE, designated SEQ ID:10595, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27933] A function of VGAM686 is therefore inhibition of COX11 Homolog, Cytochrome C Oxidase Assembly Protein (yeast) (COX11, Accession NM\_004375). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COX11. UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 7 (GalNAc-T7) (GALNT7, Accession NM\_017423) is another VGAM686 host target gene. GALNT7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GALNT7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GALNT7 BINDING SITE, designated SEQ ID:18880, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27934] Another function of VGAM686 is therefore inhibition of UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 7 (GalNAc-T7) (GALNT7, Accession NM\_017423). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GALNT7. BTB (POZ)

Domain Containing 1 (BTBD1, Accession NM\_025238) is another VGAM686 host target gene. BTBD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BTBD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BTBD1 BINDING SITE, designated SEQ ID:24922, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27935] Another function of VGAM686 is therefore inhibition of BTB (POZ) Domain Containing 1 (BTBD1, Accession NM\_025238). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BTBD1. DKFZP564D166 (Accession NM\_030658) is another VGAM686 host target gene. DKFZP564D166 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564D166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564D166 BINDING SITE, designated SEQ ID:24990, to the nucleotide

sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27936] Another function of VGAM686 is therefore inhibition of DKFZP564D166 (Accession NM\_030658). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564D166. FLJ23053 (Accession NM\_022907) is another VGAM686 host target gene. FLJ23053 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23053, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23053 BINDING SITE, designated SEQ ID:23205, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27937] Another function of VGAM686 is therefore inhibition of FLJ23053 (Accession NM\_022907). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23053. KH Domain Containing, RNA Binding, Signal Transduction Associated 1 (KHDRBS1, Accession NM\_006559) is another VGAM686 host target gene. KHDRBS1 BINDING SITE is

HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KHDRBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KHDRBS1 BINDING SITE, designated SEQ ID:13329, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27938] Another function of VGAM686 is therefore inhibition of KH Domain Containing, RNA Binding, Signal Transduction Associated 1 (KHDRBS1, Accession NM\_006559). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KHDRBS1. KIAA1393 (Accession XM\_050793) is another VGAM686 host target gene. KIAA1393 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1393, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1393 BINDING SITE, designated SEQ ID:35690, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27939] Another function of VGAM686 is therefore inhibition of KIAA1393 (Accession XM\_050793). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1393. PORIMIN (Accession NM\_052932) is another VGAM686 host target gene. PORIMIN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PORIMIN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PORIMIN BINDING SITE, designated SEQ ID:27490, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27940] Another function of VGAM686 is therefore inhibition of PORIMIN (Accession NM\_052932). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PORIMIN. RNAH (Accession XM\_030392) is another VGAM686 host target gene. RNAH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNAH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of RNAH BINDING SITE, designated SEQ ID:31038, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27941] Another function of VGAM686 is therefore inhibition of RNAH (Accession XM\_030392). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNAH. LOC158714 (Accession XM\_088650) is another VGAM686 host target gene. LOC158714 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158714, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158714 BINDING SITE, designated SEQ ID:39886, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27942] Another function of VGAM686 is therefore inhibition of LOC158714 (Accession XM\_088650). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC158714. LOC221362 (Accession XM\_168093) is another VGAM686 host target gene. LOC221362 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221362, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221362 BINDING SITE, designated SEQ ID:45023, to the nucleotide sequence of VGAM686 RNA, herein designated VGAM RNA, also designated SEQ ID:3397.

[27943] Another function of VGAM686 is therefore inhibition of LOC221362 (Accession XM\_168093). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221362. LOC255158 (Accession XM\_171213) is another VGAM686 host target gene. LOC255158 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255158, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255158 BINDING SITE, designated SEQ ID:46000, to the nucleotide sequence of VGAM686 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3397.

[27944] Another function of VGAM686 is therefore inhibition of LOC255158 (Accession XM\_171213). Accordingly, utilities of VGAM686 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255158. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 687 (VGAM687) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27945] VGAM687 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM687 was detected is described hereinabove with reference to Figs. 1–8.

[27946] VGAM687 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM687 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27947] VGAM687 gene encodes a VGAM687 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM687 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM687 precursor RNA is designated SEQ ID:673, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:673 is located at position 14557 relative to the genome of Human Coronavirus 229E.

[27948] VGAM687 precursor RNA folds onto itself, forming VGAM687 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27949] An enzyme complex designated DICER COMPLEX, `dices` the VGAM687 folded precursor RNA into VGAM687 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM687 RNA is designated SEQ ID:3398, and is provided hereinbelow with reference to the sequence listing part.

[27950] VGAM687 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM687 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM687 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27951] VGAM687 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM687 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM687 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM687 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM687 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[27952] The complementary binding of VGAM687 RNA, herein designated VGAM RNA, to host target binding sites on VGAM687 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM687 host target RNA into VGAM687 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27953] It is appreciated that VGAM687 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM687 host target genes. The mRNA of

each one of this plurality of VGAM687 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM687 RNA, herein designated VGAM RNA, and which when bound by VGAM687 RNA causes inhibition of translation of respective one or more VGAM687 host target proteins.

[27954] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM687 gene, herein designated VGAM GENE, on one or more VGAM687 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[27955] It is yet further appreciated that a function of VGAM687 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM687 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM687 correlate with, and may be deduced from, the identity of the host target genes which VGAM687 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27956] Nucleotide sequences of the VGAM687 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM687 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM687 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM687 are further described hereinbelow with reference to Table 1.

[27957] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM687 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM687 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[27958] As mentioned hereinabove with reference to Fig. 1, a function of VGAM687 gene, herein designated VGAM is inhibition of expression of VGAM687 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM687 correlate with, and may be deduced from, the identity of the target genes which VGAM687 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27959] KIAA0022 (Accession NM\_014880) is a VGAM687 host target gene. KIAA0022 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0022, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0022 BINDING SITE, designated SEQ ID:17024, to the nucleotide sequence of VGAM687 RNA, herein designated VGAM RNA, also designated SEQ ID:3398.

[27960] A function of VGAM687 is therefore inhibition of KIAA0022 (Accession NM\_014880). Accordingly, utilities of VGAM687 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with KIAA0022. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 688 (VGAM688) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27961] VGAM688 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM688 was detected is described hereinabove with reference to Figs. 1–8.

[27962] VGAM688 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM688 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27963] VGAM688 gene encodes a VGAM688 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM688 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM688 precursor RNA is designated SEQ

ID:674, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:674 is located at position 7056 relative to the genome of Human Coronavirus 229E.

[27964] VGAM688 precursor RNA folds onto itself, forming VGAM688 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27965] An enzyme complex designated DICER COMPLEX, `dices` the VGAM688 folded precursor RNA into VGAM688 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM688 RNA is designated SEQ ID:3399, and is provided hereinbelow with reference to the sequence

listing part.

[27966] VGAM688 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM688 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM688 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27967] VGAM688 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM688 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM688 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM688 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM688 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27968] The complementary binding of VGAM688 RNA, herein designated VGAM RNA, to host target binding sites on VGAM688 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM688 host target RNA into VGAM688 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[27969] It is appreciated that VGAM688 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM688 host target genes. The mRNA of each one of this plurality of VGAM688 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM688 RNA, herein designated VGAM

RNA, and which when bound by VGAM688 RNA causes inhibition of translation of respective one or more VGAM688 host target proteins.

[27970] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM688 gene, herein designated VGAM GENE, on one or more VGAM688 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27971] It is yet further appreciated that a function of VGAM688 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM688 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM688 correlate with, and may be deduced from, the identity of the host target genes which VGAM688 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27972] Nucleotide sequences of the VGAM688 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM688 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM688 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM688 are further described hereinbelow with reference to Table 1.

[27973] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM688 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM688 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27974] As mentioned hereinabove with reference to Fig. 1, a function of VGAM688 gene, herein designated VGAM is

inhibition of expression of VGAM688 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM688 correlate with, and may be deduced from, the identity of the target genes which VGAM688 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27975] LANGERIN (Accession NM\_015717) is a VGAM688 host target gene. LANGERIN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LANGERIN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LANGERIN BINDING SITE, designated SEQ ID:17930, to the nucleotide sequence of VGAM688 RNA, herein designated VGAM RNA, also designated SEQ ID:3399.

[27976] A function of VGAM688 is therefore inhibition of LANGERIN (Accession NM\_015717), a gene which could be involved in endocytosis. Accordingly, utilities of VGAM688 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LANGERIN. The function of LANGERIN has been established by previous studies. Dendritic cells (DCs) process exogenous antigen

within major histocompatibility complex (MHC) class II-rich endosome/lysosome compartments to allow presentation to CD4 (OMIM Ref. No. 186940)-positive T cells. They also route exogenous antigen into the MHC class I pathway for presentation to CD8 (OMIM Ref. No. 186910)-positive T cells by a mechanism known as cross priming. Langerhans cells (LCs) are immature DCs of the epidermis and mucosal tissues; see 604856. Birbeck granules (BGs) are organelles in the cytoplasm of LCs that have a 'tennis racket' appearance consisting of superimposed and zippered membranes. Using a monoclonal antibody to screen a DC cDNA library expressed in fibroblasts, Valladeau et al. (2000) isolated a cDNA encoding a 328-amino acid type II transmembrane protein, which they named langerin. Sequence analysis identified a calcium dependent (OMIM Ref. No. C-type) lectin domain; a glu-pro-asn motif, predicting mannose recognition; a proline-rich potential signal-transduction motif; and 2 potential N-glycosylation sites. The langerin protein is 66% identical to its mouse homolog (Valladeau et al., 2002). RT-PCR analysis detected abundant expression of langerin in freshly isolated LCs. Lower levels were detected in cultured DCs, and no expression was detected in



monocytes, T lymphocytes, granulocytes, B lymphocytes, and skin basal cells. Northern blot analysis of normal tissues detected strong expression of a 2.0-kb langerin transcript in lung but not in pancreas, kidney, skeletal muscle, liver, placenta, brain, heart, bone marrow, and peripheral blood leukocytes. Western blot analysis of DCs cultured with transforming growth factor-beta (OMIM Ref. No. 190180) showed expression of a 40-kD protein, similar to the predicted molecular mass. Confocal microscopy detected langerin at the LC cell surface and also in the cytoplasm. Electron microscopy detected langerin inside intracellular BGs but not in MHC class II-rich compartments. Valladeau et al. (2000) showed that expression of langerin induces membrane superimposition and zippering to produce BGs. They proposed that mannose binding by langerin leads to internalization of antigen into BGs and possibly access to the class I pathway.

[27977] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[27978] Valladeau, J.; Clair-Moninot, V.; Dezutter-Dambuyant, C.; Pin, J.-J.; Kissenpfennig, A.; Mattei, M.-G.; Ait-Yahia, S.; Bates, E. E. M.; Malissen, B.; Koch, F.; Fossiez, F.; Romani,

N.; Lebecque, S.; Saeland, S. : Identification of mouse langerin/CD207 in Langerhans cells and some dendritic cells of lymphoid tissues. J. Immun. 168: 782–792, 2002. ; and

[27979] Valladeau, J.; Ravel, O.; Dezutter–Dambuyant, C.; Moore, K.; Kleijmeer, M.; Liu, Y.; Duvert–Frances, V.; Vincent, C.; Schmitt, D.; Davoust, J.; Caux, C.; Lebecque, S.; Saeland, S. : Lan.

[27980] Further studies establishing the function and utilities of LANGERIN are found in John Hopkins OMIM database record ID 604862, and in cited publications numbered 7298–7299 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Midline 1 (Opitz/BBB syndrome) (MID1, Accession NM\_000381) is another VGAM688 host target gene. MID1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MID1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MID1 BINDING SITE, designated SEQ ID:5956, to the nucleotide sequence of VGAM688 RNA, herein designated VGAM RNA, also designated SEQ ID:3399.

[27981] Another function of VGAM688 is therefore inhibition of

Midline 1 (Opitz/BBB syndrome) (MID1, Accession NM\_000381). Accordingly, utilities of VGAM688 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MID1. KIAA0461 (Accession XM\_047883) is another VGAM688 host target gene.

KIAA0461 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0461, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0461 BINDING SITE, designated SEQ ID:35076, to the nucleotide sequence of VGAM688 RNA, herein designated VGAM RNA, also designated SEQ ID:3399.

[27982] Another function of VGAM688 is therefore inhibition of KIAA0461 (Accession XM\_047883). Accordingly, utilities of VGAM688 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0461. LOC131000 (Accession XM\_067145) is another VGAM688 host target gene. LOC131000 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC131000, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC131000 BINDING SITE, designated SEQ ID:37350, to the nucleotide sequence of VGAM688 RNA, herein designated VGAM RNA, also designated SEQ ID:3399.

[27983] Another function of VGAM688 is therefore inhibition of LOC131000 (Accession XM\_067145). Accordingly, utilities of VGAM688 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC131000. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 689 (VGAM689) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[27984] VGAM689 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM689 was detected is described hereinabove with reference to Figs. 1–8.

[27985] VGAM689 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM689 host target gene, herein designated

VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[27986] VGAM689 gene encodes a VGAM689 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM689 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM689 precursor RNA is designated SEQ ID:675, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:675 is located at position 19049 relative to the genome of Human Coronavirus 229E.

[27987] VGAM689 precursor RNA folds onto itself, forming VGAM689 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[27988] An enzyme complex designated DICER COMPLEX, `dices` the VGAM689 folded precursor RNA into VGAM689 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 53%) nucleotide sequence of VGAM689 RNA is designated SEQ ID:3400, and is provided hereinbelow with reference to the sequence listing part.

[27989] VGAM689 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM689 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM689 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[27990] VGAM689 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM689 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM689 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM689 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM689 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[27991] The complementary binding of VGAM689 RNA, herein designated VGAM RNA, to host target binding sites on VGAM689 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM689 host target RNA into VGAM689 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[27992] It is appreciated that VGAM689 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM689 host target genes. The mRNA of each one of this plurality of VGAM689 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM689 RNA, herein designated VGAM RNA, and which when bound by VGAM689 RNA causes inhibition of translation of respective one or more VGAM689 host target proteins.

[27993] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM689 gene, herein designated VGAM GENE, on one or more VGAM689 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-



pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[27994] It is yet further appreciated that a function of VGAM689 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM689 correlate with, and may be deduced from, the identity of the host target genes which VGAM689 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[27995] Nucleotide sequences of the VGAM689 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM689 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM689 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM689 are further described hereinbelow with reference to Table 1.

[27996] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM689 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM689 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[27997] As mentioned hereinabove with reference to Fig. 1, a function of VGAM689 gene, herein designated VGAM is inhibition of expression of VGAM689 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM689 correlate with, and may be deduced from, the identity of the target genes which VGAM689 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[27998] Nuclear Receptor Subfamily 2, Group E, Member 1 (NR2E1, Accession NM\_003269) is a VGAM689 host target gene. NR2E1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NR2E1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR2E1 BINDING SITE, designated SEQ ID:9277, to the nucleotide sequence of VGAM689 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3400.

[27999] A function of VGAM689 is therefore inhibition of Nuclear Receptor Subfamily 2, Group E, Member 1 (NR2E1, Accession NM\_003269), a gene which may be required for brain development and be involved in the regulation of retinal development . Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR2E1. The function of NR2E1 has been established by previous studies. The product of the *Drosophila* terminal/gap gene 'tailless' (tll) is expressed in the embryonic brain and is required for brain development in flies. The tll protein is a ligand-activated nuclear receptor-type transcription factor. In 2 discrete subregions of the DNA-binding domain (DBD) that modulate the mode of DNA binding, the tll protein contains changes that distinguish it from all other nuclear receptors. Yu et al. (1994) identified the chick and mouse Tlx genes, encoding the vertebrate tll homolog. The vertebrate Tlx proteins are highly conserved, and both avian and mammalian Tlx contain the distinct tll DBD sequences. In vitro DNA-binding assays demonstrated that Tlx and tll share a target gene specificity that is unique among the nuclear receptor superfamily. Ectopic expres-

sion of chick Tlx in fly embryos caused a repression of segmentation comparable to that elicited by tll. In situ hybridization to chick and mouse embryos revealed that Tlx is expressed in the head ectoderm in early embryos. At later stages, cells expressing Tlx are localized in the ventricular zone of the neuroepithelial layer, suggesting that Tlx is involved in transcriptional control in undifferentiated neuroepithelial cells in the anterior regions of the developing vertebrate brain. By searching for genes located within the 6q21–q23 region of minimal deletion (RMD) associated with hematologic malignancies, Jackson et al. (1998) identified the human TLX homolog, also called NR2E1. The TLX gene contains 9 exons and spans 24 kb. By a combination of direct sequencing, exon trapping, and library screening, they isolated human TLX cDNAs. The predicted 386–amino acid human protein shares 97% and 99% identity with chick and mouse TLX, respectively. The highest degree of similarity between TLX and *Drosophila* tll is within the DBDs and the ligand-binding domains (LBDs) of the proteins. Northern blot analysis revealed that the approximately 3.9–kb TLX mRNA is expressed exclusively in brain.

[28000] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [28001] Jackson, A.; Panayiotidis, P.; Foroni, L. : The human homologue of the *Drosophila* tailless gene (TLX): characterization and mapping to a region of common deletion in human lymphoid leukemia on chromosome 6q21. *Genomics* 50: 34–43, 1998. ; and
- [28002] Yu, R. T.; McKeown, M.; Evans, R. M.; Umesono, K. : Relationship between *Drosophila* gap gene tailless and a vertebrate nuclear receptor Tlx. *Nature* 370: 375–379, 1994.
- [28003] Further studies establishing the function and utilities of NR2E1 are found in John Hopkins OMIM database record ID 603849, and in cited publications numbered 2416–2418 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Synaptogyrin 1 (SYNGR1, Accession NM\_004711) is another VGAM689 host target gene. SYNGR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SYNGR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYNGR1 BINDING SITE, designated SEQ ID:11059, to the nucleotide

sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28004] Another function of VGAM689 is therefore inhibition of Synaptogyrin 1 (SYNGR1, Accession NM\_004711), a gene which belongs to transmembrane synaptic vesicle protein and may function in membrane recycling. Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYNGR1. The function of SYNGR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM107. Chromosome 12 Open Reading Frame 2 (C12orf2, Accession XM\_096040) is another VGAM689 host target gene. C12orf2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C12orf2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C12orf2 BINDING SITE, designated SEQ ID:40291, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28005] Another function of VGAM689 is therefore inhibition of

Chromosome 12 Open Reading Frame 2 (C12orf2, Accession XM\_096040). Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C12orf2. Chromosome 20 Open Reading Frame 21 (C20orf21, Accession NM\_017798) is another VGAM689 host target gene. C20orf21 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf21, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf21 BINDING SITE, designated SEQ ID:19441, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28006] Another function of VGAM689 is therefore inhibition of Chromosome 20 Open Reading Frame 21 (C20orf21, Accession NM\_017798). Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf21. MGC17330 (Accession NM\_052880) is another VGAM689 host target gene. MGC17330 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of

mRNA encoded by MGC17330, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC17330 BINDING SITE, designated SEQ ID:27459, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28007] Another function of VGAM689 is therefore inhibition of MGC17330 (Accession NM\_052880). Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC17330. LOC150225 (Accession XM\_097870) is another VGAM689 host target gene. LOC150225 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150225, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150225 BINDING SITE, designated SEQ ID:41193, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28008] Another function of VGAM689 is therefore inhibition of LOC150225 (Accession XM\_097870). Accordingly, utilities



of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150225. LOC150481 (Accession XM\_086929) is another VGAM689 host target gene. LOC150481 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150481, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150481 BINDING SITE, designated SEQ ID:38982, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28009] Another function of VGAM689 is therefore inhibition of LOC150481 (Accession XM\_086929). Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150481. LOC152316 (Accession XM\_098185) is another VGAM689 host target gene. LOC152316 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC152316 BINDING SITE, designated SEQ ID:41455, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28010] Another function of VGAM689 is therefore inhibition of LOC152316 (Accession XM\_098185). Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152316. LOC158191 (Accession XM\_088505) is another VGAM689 host target gene. LOC158191 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158191, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158191 BINDING SITE, designated SEQ ID:39760, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28011] Another function of VGAM689 is therefore inhibition of LOC158191 (Accession XM\_088505). Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158191. LOC90072 (Accession XM\_028702) is another VGAM689 host target gene. LOC90072 BINDING

SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90072, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90072 BINDING SITE, designated SEQ ID:30732, to the nucleotide sequence of VGAM689 RNA, herein designated VGAM RNA, also designated SEQ ID:3400.

[28012] Another function of VGAM689 is therefore inhibition of LOC90072 (Accession XM\_028702). Accordingly, utilities of VGAM689 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90072. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 690 (VGAM690) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28013] VGAM690 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM690 was detected is described hereinabove with reference to Figs. 1-8.

[28014] VGAM690 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM690 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28015] VGAM690 gene encodes a VGAM690 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM690 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM690 precursor RNA is designated SEQ ID:676, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:676 is located at position 5793 relative to the genome of Human Coronavirus 229E.

[28016] VGAM690 precursor RNA folds onto itself, forming VGAM690 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[28017] An enzyme complex designated DICER COMPLEX, `dices` the VGAM690 folded precursor RNA into VGAM690 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM690 RNA is designated SEQ ID:3401, and is provided hereinbelow with reference to the sequence listing part.

[28018] VGAM690 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM690 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM690 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28019] VGAM690 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM690 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM690 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM690 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM690 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28020] The complementary binding of VGAM690 RNA, herein designated VGAM RNA, to host target binding sites on VGAM690 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM690 host target RNA into VGAM690 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28021] It is appreciated that VGAM690 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM690 host target genes. The mRNA of each one of this plurality of VGAM690 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM690 RNA, herein designated VGAM RNA, and which when bound by VGAM690 RNA causes inhibition of translation of respective one or more VGAM690 host target proteins.

[28022] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM690 gene, herein designated VGAM GENE, on one or more VGAM690 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28023] It is yet further appreciated that a function of VGAM690 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM690 correlate with, and may be deduced from, the identity of the host target genes which VGAM690 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28024] Nucleotide sequences of the VGAM690 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM690 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM690 folded precursor RNA, herein designated



VGAM FOLDED PRECURSOR RNA, of VGAM690 are further described hereinbelow with reference to Table 1.

[28025] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM690 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM690 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28026] As mentioned hereinabove with reference to Fig. 1, a function of VGAM690 gene, herein designated VGAM is inhibition of expression of VGAM690 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM690 correlate with, and may be deduced from, the identity of the target genes which VGAM690 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28027] Eyes Absent Homolog 2 (Drosophila) (EYA2, Accession NM\_005244) is a VGAM690 host target gene. EYA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EYA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates

the complementarity of the nucleotide sequences of EYA2 BINDING SITE, designated SEQ ID:11752, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28028] A function of VGAM690 is therefore inhibition of Eyes Absent Homolog 2 (Drosophila) (EYA2, Accession NM\_005244), a gene which may be involved in development of the eye. Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EYA2. The function of EYA2 has been established by previous studies. Abdelhak et al. (1997) identified, by positional cloning, a gene at 8q13.3, which contains mutations in patients with branchiootorenal dysplasia (BOR; 113650). The gene is a human homolog of the Drosophila 'eyes absent' (eya), and was therefore called EYA1 (OMIM Ref. No. 601653). A highly conserved 271-amino acid C-terminal region was also found in the products of 2 other human genes that were subsequently called EYA2 and EYA3 (OMIM Ref. No. 601655), demonstrating the existence of a novel gene family. Some of these other members of the EYA gene family may underlie developmental defects because Abdelhak et al. (1997) demonstrated that all 3 of these

genes are expressed in the ninth week of human development. Gene identification strategies that rely on cross-species comparison are based on the observation that functionally significant regions of the genome are highly conserved during evolution. Banfi et al. (1996) applied the power of *Drosophila* genetics to the vast resource of human cDNAs represented in the expressed sequence tag (EST) database to identify novel human genes of biologic interest. One human cDNA (GenBank H07988) showing significant homology to the gene causing the *Drosophila* mutant phenotype 'clift' ('eyes absent') was reported by Abdelhak et al. (1997) to be the EYA2 gene. Banfi et al. (1996) mapped the human gene to 20q13.1 using both fluorescence in situ hybridization and radiation hybrid mapping. Zimmerman et al. (1997) mapped the mouse *Eya2* gene to chromosome 2 in a region syntenic with human 20q13. Duncan et al. (1997) likewise mapped EYA2 to human 20q13.1 and *Eya2* to mouse chromosome 2. Duncan et al. (1997) found that *Eya2* shows a dynamic pattern of expression during mouse development. Its expression was first detected in 8.5-day embryos in the region of head ectoderm fated to become the forebrain. At later stages of development, *Eya2* was expressed in the

olfactory placode and in a variety of neural crest derivatives. In the eye, expression of Eya2 was first detected after formation of the lens vesicle. At day 17.5, the highest level of Eya2 mRNA was observed in primary lens fibers. Low levels of Eya2 expression were detected in retina, sclera, and cornea. Duncan et al. (1997) stated that, although Eya2 is expressed relatively late in eye development, it belongs to a growing list of factors that may be essential for eye development among metazoan phyla. Like members of the PAX6 gene family (see OMIM Ref. No. 607108), 'eyes absent' gene family members were probably first involved in functions not related to vision, with recruitment for visual system formation and function occurring later. Xu et al. (1997) showed that in the limbs of 10.5-day mouse embryos, Eya1 expression was largely restricted to the flexor tendons, whereas Eya2 was expressed in the extensor tendons and probably also in the ligaments of the phalanges. They demonstrated that the proline/serine/threonine-rich N-terminal regions of the protein products of the Eya1, Eya2, and Eya3 genes have transcriptional activator activity. These results supported a role for the Eya genes in connective tissue patterning in the limbs.

[28029] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28030] Abdelhak, S.; Kalatzis, V.; Heilig, R.; Compain, S.; Samson, D.; Vincent, C.; Weil, D.; Cruaud, C.; Sahly, I.; Leibovici, M.; Bitner-Glindzicz, M.; Francis, M.; Lacombe, D.; Vigneron, J.; Charachon, R.; Boven, K.; Bedbeder, P.; Van Rege-morter, N.; Weissenbach, J.; Petit, C. : A human homo-logue of the Drosophila eyes absent gene underlies bran-chio-oto-renal (BOR) syndrome and identifies a novel gene family. Nature Genet. 15: 157–164, 1997. ; and

[28031] Xu, P.-X.; Cheng, J.; Epstein, J. A.; Maas, R. L. : Mouse Eya genes are expressed during limb tendon development and encode a transcriptional activation function. Proc. Nat. Acad. Sci. 9.

[28032] Further studies establishing the function and utilities of EYA2 are found in John Hopkins OMIM database record ID 601654, and in cited publications numbered 12159–6024 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Fam-ily 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) Trans-porter), Member 3 (SLC35A3, Accession NM\_012243) is another VGAM690 host target gene. SLC35A3 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC35A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC35A3 BINDING SITE, designated SEQ ID:14549, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28033] Another function of VGAM690 is therefore inhibition of Solute Carrier Family 35 (UDP-N-acetylglucosamine (UDP-GlcNAc) Transporter), Member 3 (SLC35A3, Accession NM\_012243). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC35A3. FLJ32499 (Accession NM\_144607) is another VGAM690 host target gene. FLJ32499 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ32499, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32499 BINDING SITE, designated SEQ ID:29421, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ

ID:3401.

[28034] Another function of VGAM690 is therefore inhibition of FLJ32499 (Accession NM\_144607). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32499. KIAA1233 (Accession XM\_032181) is another VGAM690 host target gene. KIAA1233 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1233, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1233 BINDING SITE, designated SEQ ID:31590, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28035] Another function of VGAM690 is therefore inhibition of KIAA1233 (Accession XM\_032181). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1233. KIAA1910 (Accession XM\_055514) is another VGAM690 host target gene. KIAA1910 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1910, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1910 BINDING SITE, designated SEQ ID:36284, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28036] Another function of VGAM690 is therefore inhibition of KIAA1910 (Accession XM\_055514). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1910. MGC19556 (Accession NM\_033551) is another VGAM690 host target gene. MGC19556 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC19556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC19556 BINDING SITE, designated SEQ ID:27313, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28037] Another function of VGAM690 is therefore inhibition of MGC19556 (Accession NM\_033551). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with MGC19556. LOC150606 (Accession XM\_097928) is another VGAM690 host target gene. LOC150606 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC150606, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150606 BINDING SITE, designated SEQ ID:41232, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28038] Another function of VGAM690 is therefore inhibition of LOC150606 (Accession XM\_097928). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150606. LOC221683 (Accession XM\_168089) is another VGAM690 host target gene. LOC221683 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221683, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221683 BINDING SITE, designated SEQ ID:45003, to

the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28039] Another function of VGAM690 is therefore inhibition of LOC221683 (Accession XM\_168089). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221683. LOC93589 (Accession XM\_052387) is another VGAM690 host target gene. LOC93589 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93589, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93589 BINDING SITE, designated SEQ ID:35976, to the nucleotide sequence of VGAM690 RNA, herein designated VGAM RNA, also designated SEQ ID:3401.

[28040] Another function of VGAM690 is therefore inhibition of LOC93589 (Accession XM\_052387). Accordingly, utilities of VGAM690 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93589. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 691 (VGAM691) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28041] VGAM691 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM691 was detected is described hereinabove with reference to Figs. 1–8.

[28042] VGAM691 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM691 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28043] VGAM691 gene encodes a VGAM691 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM691 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM691 precursor RNA is designated SEQ ID:677, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:677 is located at position 13850 relative to the genome of Human Coronavirus 229E.

[28044] VGAM691 precursor RNA folds onto itself, forming VGAM691 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28045] An enzyme complex designated DICER COMPLEX, `dices` the VGAM691 folded precursor RNA into VGAM691 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM691 RNA is designated SEQ ID:3402, and is provided hereinbelow with reference to the sequence listing part.

[28046] VGAM691 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM691 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM691 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28047] VGAM691 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM691 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM691 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM691 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM691 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28048] The complementary binding of VGAM691 RNA, herein designated VGAM RNA, to host target binding sites on VGAM691 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM691 host target RNA into VGAM691 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28049] It is appreciated that VGAM691 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM691 host target genes. The mRNA of each one of this plurality of VGAM691 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM691 RNA, herein designated VGAM RNA, and which when bound by VGAM691 RNA causes inhibition of translation of respective one or more VGAM691 host target proteins.

[28050] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM691 gene, herein designated VGAM GENE, on one or more VGAM691 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28051] It is yet further appreciated that a function of VGAM691 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM691 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM691 correlate with, and may be deduced from, the identity of

the host target genes which VGAM691 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28052] Nucleotide sequences of the VGAM691 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM691 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM691 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM691 are further described hereinbelow with reference to Table 1.

[28053] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM691 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM691 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28054] As mentioned hereinabove with reference to Fig. 1, a function of VGAM691 gene, herein designated VGAM is inhibition of expression of VGAM691 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM691 correlate with, and may be deduced from, the identity of the target genes which VGAM691



binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28055] Glutamate Decarboxylase 1 (brain, 67kDa) (GAD1, Accession NM\_000817) is a VGAM691 host target gene. GAD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAD1 BINDING SITE, designated SEQ ID:6479, to the nucleotide sequence of VGAM691 RNA, herein designated VGAM RNA, also designated SEQ ID:3402.

[28056] A function of VGAM691 is therefore inhibition of Glutamate Decarboxylase 1 (brain, 67kDa) (GAD1, Accession NM\_000817), a gene which catalyzes the conversion of glutamic acid to gamma-aminobutyric acid. Accordingly, utilities of VGAM691 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAD1. The function of GAD1 has been established by previous studies. Using a genomic probe from a human fetal brain library, Sparkes et al. (1987) probed the DNA of a mouse/human somatic cell hybrid panel and assigned the GAD gene to human chromosome 2. Kelly et al. (1992)

confirmed the assignment of GAD1 to chromosome 2, using PCR to amplify specifically the human sequence in rodent/human somatic cell hybrid DNAs. They also reported the full nucleotide sequence of the cDNA and the deduced amino acid sequence. Bu et al. (1992) mapped the GAD1 gene to 2q31 by in situ hybridization of fluorescently labeled GAD probes to human chromosomes. They demonstrated that the GAD1 gene encodes a polypeptide of 67,000 molecular weight, with 594 amino acid residues. The GAD2 gene (OMIM Ref. No. 138275), located on 10p11.23, encodes a polypeptide of 65,000 molecular weight (GAD65), with 585 amino acid residues. Brilliant et al. (1990) showed by Southern analysis of mouse-hamster hybrid cells and by interspecific backcrosses and recombinant inbred strains that the mouse equivalent (Gad1) is located on chromosome 2 and that an apparent pseudogene is located on mouse chromosome 10. The mouse Gad1 locus is part of a conserved homology between mouse chromosome 2 and human 2q. By in situ hybridization, Edelhoff et al. (1993) also assigned GAD1 to human 2q31 and to mouse chromosome 2D in a known region of conservation between human and mouse. Animal model experiments lend further support to the func-

tion of GAD1. The remaining exon–intron boundaries occur at identical positions in the 2 cDNAs, suggesting that they derive from a common ancestral GAD gene. In addition to its role as an inhibitory neurotransmitter, GABA is presumed to be involved in the development and plasticity of the nervous system. GABA is synthesized by glutamic acid decarboxylase, but the respective roles of its 2 isoforms, GAD65 and GAD67, had not been determined. Asada et al. (1996, 1997) undertook the selective elimination of each GAD isoform by gene targeting to clarify this issue. Asada et al. (1996) found that GAD65  $-/-$  mice showed no change in brain GABA content or animal behavior, except for a slight increase in susceptibility to seizures. Asada et al. (1997) produced GAD67  $-/-$  mice. These mice were born at the expected frequency but died of severe cleft palate during the first morning after birth. GAD activities and GABA contents were reduced to 20 and 7%, respectively, in the cerebral cortex of the newborn GAD67  $-/-$  mice. Their brains, however, did not show any discernible defects. Previous pharmacologic and genetic investigations suggested the involvement of GABA in palate formation, but this was the first demonstration of a role for GAD67–derived GABA in the development of non–

neural tissue. Independently, Condie et al. (1997) found defects in the formation of the palate in mice with a targeted mutation in the gene encoding GAD67. Previous observations had suggested a role of GABA in palate development. Analysis of mice with mutations in the beta-3 gamma-GABA receptor (GABRB3; 137192) had demonstrated that these mutations are associated with cleft secondary palate in mice. The phenotype in the GABRB3 mutants showed that this gene is somehow involved in palate development but did not demonstrate that GABA is the ligand involved in this particular function. The results of Condie et al. (1997), demonstrating a similar phenotype between the receptor and ligand mutations, demonstrated a role for GABA signaling in normal palate development.

[28057] It is appreciated that the abovementioned animal model for GAD1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[28058] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28059] Asada, H.; Kawamura, Y.; Maruyama, K.; Kume, H.; Ding, R.-G.; Ji, F. Y.; Kanbara, N.; Kuzume, H.; Sanbo, M.; Yagi,

T.; Obata, K. : Mice lacking the 65 kDa isoform of glutamic acid decarboxylase (GAD65) maintain normal levels of GAD67 and GABA in their brains but are susceptible to seizures. *Biochem. Biophys. Res. Commun.* 229: 891–895, 1996. ; and

[28060] Scriver, C. R.; Hutchison, J. H. : The vitamin B6 deficiency syndrome in human infancy: biochemical and clinical observations. *Pediatrics* 31: 240–250, 1963.

[28061] Further studies establishing the function and utilities of GAD1 are found in John Hopkins OMIM database record ID 605363, and in cited publications numbered 11924–6634, 11925–6636, 11926–6639, 1241–124 and 6640 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ22028 (Accession NM\_024854) is another VGAM691 host target gene. FLJ22028 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22028 BINDING SITE, designated SEQ ID:24284, to the nucleotide sequence of VGAM691 RNA, herein designated VGAM RNA, also designated SEQ

ID:3402.

- [28062] Another function of VGAM691 is therefore inhibition of FLJ22028 (Accession NM\_024854). Accordingly, utilities of VGAM691 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22028. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 692 (VGAM692) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [28063] VGAM692 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM692 was detected is described hereinabove with reference to Figs. 1–8.
- [28064] VGAM692 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM692 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.
- [28065] VGAM692 gene encodes a VGAM692 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM692

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM692 precursor RNA is designated SEQ ID:678, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:678 is located at position 6444 relative to the genome of Human Coronavirus 229E.

[28066] VGAM692 precursor RNA folds onto itself, forming VGAM692 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28067] An enzyme complex designated DICER COMPLEX, `dices` the VGAM692 folded precursor RNA into VGAM692 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 40%) nucleotide sequence of VGAM692 RNA is designated SEQ ID:3403, and is provided hereinbelow with reference to the sequence listing part.

[28068] VGAM692 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM692 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM692 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28069] VGAM692 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM692 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM692 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the



number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM692 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM692 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28070] The complementary binding of VGAM692 RNA, herein designated VGAM RNA, to host target binding sites on VGAM692 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM692 host target RNA into VGAM692 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28071] It is appreciated that VGAM692 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM692 host target genes. The mRNA of each one of this plurality of VGAM692 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM692 RNA, herein designated VGAM RNA, and which when bound by VGAM692 RNA causes inhibition of translation of respective one or more VGAM692 host target proteins.

[28072] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM692 gene, herein designated VGAM GENE, on one or more VGAM692 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28073] It is yet further appreciated that a function of VGAM692 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM692 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM692 correlate with, and may be deduced from, the identity of the host target genes which VGAM692 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28074] Nucleotide sequences of the VGAM692 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM692 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM692 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM692 are further described hereinbelow with reference to Table 1.

[28075] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM692 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM692 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[28076] As mentioned hereinabove with reference to Fig. 1, a function of VGAM692 gene, herein designated VGAM is inhibition of expression of VGAM692 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM692 correlate with, and may be deduced from, the identity of the target genes which VGAM692 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28077] CGI-142 (Accession NM\_016073) is a VGAM692 host target gene. CGI-142 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CGI-142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CGI-142 BINDING SITE, designated SEQ ID:18145, to the nucleotide sequence of VGAM692 RNA, herein designated VGAM RNA, also designated SEQ ID:3403.

[28078] A function of VGAM692 is therefore inhibition of CGI-142 (Accession NM\_016073). Accordingly, utilities of VGAM692 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CGI-142.

FLJ10701 (Accession NM\_018183) is another VGAM692 host target gene. FLJ10701 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10701, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10701 BINDING SITE, designated SEQ ID:20022, to the nucleotide sequence of VGAM692 RNA, herein designated VGAM RNA, also designated SEQ ID:3403.

[28079] Another function of VGAM692 is therefore inhibition of FLJ10701 (Accession NM\_018183). Accordingly, utilities of VGAM692 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10701. KIAA1363 (Accession XM\_045056) is another VGAM692 host target gene. KIAA1363 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1363, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1363 BINDING SITE, designated SEQ ID:34331, to the nucleotide sequence of VGAM692 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3403.

[28080] Another function of VGAM692 is therefore inhibition of KIAA1363 (Accession XM\_045056). Accordingly, utilities of VGAM692 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1363. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 693 (VGAM693) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28081] VGAM693 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM693 was detected is described hereinabove with reference to Figs. 1–8.

[28082] VGAM693 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM693 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28083] VGAM693 gene encodes a VGAM693 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM693 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM693 precursor RNA is designated SEQ ID:679, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:679 is located at position 4759 relative to the genome of Human Coronavirus 229E.

[28084] VGAM693 precursor RNA folds onto itself, forming VGAM693 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28085] An enzyme complex designated DICER COMPLEX, `dices` the VGAM693 folded precursor RNA into VGAM693 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 58%) nucleotide sequence of VGAM693 RNA is designated SEQ ID:3404, and is provided hereinbelow with reference to the sequence listing part.

[28086] VGAM693 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM693 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM693 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28087] VGAM693 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM693 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM693 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and



BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM693 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM693 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[28088] The complementary binding of VGAM693 RNA, herein designated VGAM RNA, to host target binding sites on VGAM693 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM693 host target RNA into VGAM693 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28089] It is appreciated that VGAM693 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM693 host target genes. The mRNA of

each one of this plurality of VGAM693 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM693 RNA, herein designated VGAM RNA, and which when bound by VGAM693 RNA causes inhibition of translation of respective one or more VGAM693 host target proteins.

[28090] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM693 gene, herein designated VGAM GENE, on one or more VGAM693 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[28091] It is yet further appreciated that a function of VGAM693 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM693 correlate with, and may be deduced from, the identity of the host target genes which VGAM693 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28092] Nucleotide sequences of the VGAM693 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM693 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM693 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM693 are further described hereinbelow with reference to Table 1.

[28093] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM693 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM693 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[28094] As mentioned hereinabove with reference to Fig. 1, a function of VGAM693 gene, herein designated VGAM is inhibition of expression of VGAM693 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM693 correlate with, and may be deduced from, the identity of the target genes which VGAM693 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28095] Contactin Associated Protein-like 2 (CNTNAP2, Accession NM\_014141) is a VGAM693 host target gene. CNTNAP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNTNAP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNTNAP2 BINDING SITE, designated SEQ ID:15423, to the nucleotide sequence of VGAM693 RNA, herein designated VGAM RNA, also designated SEQ ID:3404.

[28096] A function of VGAM693 is therefore inhibition of Contactin Associated Protein-like 2 (CNTNAP2, Accession

NM\_014141). Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNTNAP2. Protocadherin Beta 12 (PCDHB12, Accession NM\_018932) is another VGAM693 host target gene. PCDHB12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHB12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHB12 BINDING SITE, designated SEQ ID:21003, to the nucleotide sequence of VGAM693 RNA, herein designated VGAM RNA, also designated SEQ ID:3404.

[28097] Another function of VGAM693 is therefore inhibition of Protocadherin Beta 12 (PCDHB12, Accession NM\_018932). Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHB12. Protocadherin Beta 7 (PCDHB7, Accession NM\_018940) is another VGAM693 host target gene. PCDHB7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHB7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of PCDHB7 BINDING SITE, designated SEQ ID:21009, to the nucleotide sequence of VGAM693 RNA, herein designated VGAM RNA, also designated SEQ ID:3404.

[28098] Another function of VGAM693 is therefore inhibition of Protocadherin Beta 7 (PCDHB7, Accession NM\_018940). Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHB7. FLJ21302 (Accession NM\_022901) is another VGAM693 host target gene. FLJ21302 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21302, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21302 BINDING SITE, designated SEQ ID:23185, to the nucleotide sequence of VGAM693 RNA, herein designated VGAM RNA, also designated SEQ ID:3404.

[28099] Another function of VGAM693 is therefore inhibition of FLJ21302 (Accession NM\_022901). Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ21302. FLJ22557 (Accession NM\_024713) is another VGAM693 host target gene. FLJ22557 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22557, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22557 BINDING SITE, designated SEQ ID:24039, to the nucleotide sequence of VGAM693 RNA, herein designated VGAM RNA, also designated SEQ ID:3404.

[28100] Another function of VGAM693 is therefore inhibition of FLJ22557 (Accession NM\_024713). Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22557. KIAA1228 (Accession XM\_036408) is another VGAM693 host target gene. KIAA1228 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1228 BINDING SITE, designated SEQ ID:32448, to the nucleotide sequence of

VGAM693 RNA, herein designated VGAM RNA, also designated SEQ ID:3404.

[28101] Another function of VGAM693 is therefore inhibition of KIAA1228 (Accession XM\_036408). Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1228. Protocadherin 10 (PCDH10, Accession NM\_032961) is another VGAM693 host target gene. PCDH10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDH10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDH10 BINDING SITE, designated SEQ ID:26772, to the nucleotide sequence of VGAM693 RNA, herein designated VGAM RNA, also designated SEQ ID:3404.

[28102] Another function of VGAM693 is therefore inhibition of Protocadherin 10 (PCDH10, Accession NM\_032961). Accordingly, utilities of VGAM693 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH10. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral



gene of the present invention, referred to here as Viral Genomic Address Messenger 694 (VGAM694) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28103] VGAM694 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM694 was detected is described hereinabove with reference to Figs. 1–8.

[28104] VGAM694 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM694 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28105] VGAM694 gene encodes a VGAM694 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM694 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM694 precursor RNA is designated SEQ ID:680, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:680 is located at position 9591 relative to the genome of Human

Coronavirus 229E.

[28106] VGAM694 precursor RNA folds onto itself, forming VGAM694 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28107] An enzyme complex designated DICER COMPLEX, `dices` the VGAM694 folded precursor RNA into VGAM694 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM694 RNA is designated SEQ ID:3405, and is provided hereinbelow with reference to the sequence listing part.

[28108] VGAM694 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM694 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM694 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28109] VGAM694 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM694 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM694 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM694 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM694 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28110] The complementary binding of VGAM694 RNA, herein designated VGAM RNA, to host target binding sites on VGAM694 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM694 host target RNA into VGAM694 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28111] It is appreciated that VGAM694 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM694 host target genes. The mRNA of each one of this plurality of VGAM694 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM694 RNA, herein designated VGAM RNA, and which when bound by VGAM694 RNA causes inhibition of translation of respective one or more VGAM694 host target proteins.

[28112] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM694 gene, herein designated VGAM GENE, on one or more VGAM694 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28113] It is yet further appreciated that a function of VGAM694 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM694 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM694

correlate with, and may be deduced from, the identity of the host target genes which VGAM694 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28114] Nucleotide sequences of the VGAM694 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM694 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM694 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM694 are further described hereinbelow with reference to Table 1.

[28115] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM694 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM694 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28116] As mentioned hereinabove with reference to Fig. 1, a function of VGAM694 gene, herein designated VGAM is inhibition of expression of VGAM694 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM694 correlate with, and may be deduced

from, the identity of the target genes which VGAM694 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28117] Adenylate Cyclase 7 (ADCY7, Accession NM\_001114) is a VGAM694 host target gene. ADCY7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADCY7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADCY7 BINDING SITE, designated SEQ ID:6780, to the nucleotide sequence of VGAM694 RNA, herein designated VGAM RNA, also designated SEQ ID:3405.

[28118] A function of VGAM694 is therefore inhibition of Adenylate Cyclase 7 (ADCY7, Accession NM\_001114), a gene which is a membrane-bound,  $\text{Ca}^{2+}$ -inhibitable adenylyl cyclase. Accordingly, utilities of VGAM694 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADCY7. The function of ADCY7 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM108.EGF-like-domain, Multiple 4 (EGFL4, Accession

XM\_029883) is another VGAM694 host target gene. EGFL4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGFL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGFL4 BINDING SITE, designated SEQ ID:30963, to the nucleotide sequence of VGAM694 RNA, herein designated VGAM RNA, also designated SEQ ID:3405.

[28119] Another function of VGAM694 is therefore inhibition of EGF-like-domain, Multiple 4 (EGFL4, Accession XM\_029883). Accordingly, utilities of VGAM694 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGFL4. Glutaminase (GLS, Accession NM\_014905) is another VGAM694 host target gene. GLS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLS BINDING SITE, designated SEQ ID:17105, to the nucleotide sequence of VGAM694 RNA, herein designated VGAM RNA, also designated SEQ ID:3405.



[28120] Another function of VGAM694 is therefore inhibition of Glutaminase (GLS, Accession NM\_014905). Accordingly, utilities of VGAM694 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLS. Vanin 1 (VNN1, Accession NM\_004666) is another VGAM694 host target gene. VNN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VNN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VNN1 BINDING SITE, designated SEQ ID:11038, to the nucleotide sequence of VGAM694 RNA, herein designated VGAM RNA, also designated SEQ ID:3405.

[28121] Another function of VGAM694 is therefore inhibition of Vanin 1 (VNN1, Accession NM\_004666), a gene which may regulate steps in thymus homing and play a role in mammalian sexual development. Accordingly, utilities of VGAM694 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VNN1. The function of VNN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference

to VGAM419.LOC56920 (Accession NM\_020163) is another VGAM694 host target gene. LOC56920 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC56920, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC56920 BINDING SITE, designated SEQ ID:21380, to the nucleotide sequence of VGAM694 RNA, herein designated VGAM RNA, also designated SEQ ID:3405.

[28122] Another function of VGAM694 is therefore inhibition of LOC56920 (Accession NM\_020163). Accordingly, utilities of VGAM694 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC56920. LOC93463 (Accession XM\_051528) is another VGAM694 host target gene. LOC93463 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC93463, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93463 BINDING SITE, designated SEQ ID:35850, to the nucleotide sequence of VGAM694 RNA, herein designated

VGAM RNA, also designated SEQ ID:3405.

[28123] Another function of VGAM694 is therefore inhibition of LOC93463 (Accession XM\_051528). Accordingly, utilities of VGAM694 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93463. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 695 (VGAM695) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28124] VGAM695 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM695 was detected is described hereinabove with reference to Figs. 1–8.

[28125] VGAM695 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM695 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28126] VGAM695 gene encodes a VGAM695 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM695 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM695 precursor RNA is designated SEQ ID:681, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:681 is located at position 2788 relative to the genome of Human Coronavirus 229E.

[28127] VGAM695 precursor RNA folds onto itself, forming VGAM695 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28128] An enzyme complex designated DICER COMPLEX, `dices` the VGAM695 folded precursor RNA into VGAM695 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 51%) nucleotide sequence of VGAM695 RNA is designated SEQ ID:3406, and is provided hereinbelow with reference to the sequence listing part.

[28129] VGAM695 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM695 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM695 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[28130] VGAM695 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM695 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM695 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM695 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM695 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28131] The complementary binding of VGAM695 RNA, herein designated VGAM RNA, to host target binding sites on VGAM695 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM695 host target RNA into VGAM695 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28132] It is appreciated that VGAM695 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM695 host target genes. The mRNA of

each one of this plurality of VGAM695 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM695 RNA, herein designated VGAM RNA, and which when bound by VGAM695 RNA causes inhibition of translation of respective one or more VGAM695 host target proteins.

[28133] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM695 gene, herein designated VGAM GENE, on one or more VGAM695 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[28134] It is yet further appreciated that a function of VGAM695 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM695 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM695 correlate with, and may be deduced from, the identity of the host target genes which VGAM695 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28135] Nucleotide sequences of the VGAM695 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM695 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM695 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM695 are further described hereinbelow with reference to Table 1.

[28136] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM695 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM695 RNA, herein desig-



nated VGAM RNA, are described hereinbelow with reference to Table 2.

[28137] As mentioned hereinabove with reference to Fig. 1, a function of VGAM695 gene, herein designated VGAM is inhibition of expression of VGAM695 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM695 correlate with, and may be deduced from, the identity of the target genes which VGAM695 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28138] Estrogen Receptor 1 (ESR1, Accession NM\_000125) is a VGAM695 host target gene. ESR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESR1 BINDING SITE, designated SEQ ID:5602, to the nucleotide sequence of VGAM695 RNA, herein designated VGAM RNA, also designated SEQ ID:3406.

[28139] A function of VGAM695 is therefore inhibition of Estrogen Receptor 1 (ESR1, Accession NM\_000125), a gene which involved in hormone-mediated inhibition of gene expres-

sion. Accordingly, utilities of VGAM695 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESR1. The function of ESR1 has been established by previous studies. The estrogen receptor (ESR) is a ligand-activated transcription factor composed of several domains important for hormone binding, DNA binding, and activation of transcription. Walter et al. (1985) cloned and Greene et al. (1986) sequenced a cDNA for the entire translated portion of the messenger RNA for the estrogen receptor of MCF-7 human breast cancer cells. Expression with production of a functional protein was accomplished in Chinese hamster ovary cells. The 1,785 nucleotides of the cDNA correspond to a polypeptide of 595 amino acids and a molecular weight of 66,200 (about that estimated from other studies of the estrogen receptor). Amino acid sequence comparisons showed considerable similarities between human ESR, human GCR (OMIM Ref. No. 138040), and the putative v-erbA (OMIM Ref. No. 190120) oncogene product. Both ESR and GCR exert their effects by binding directly to an intranuclear receptor molecule that is weakly associated with nuclear components in the absence of ligand. Binding of hormone to its receptor results in conversion of the receptor-

steroid complex to a form that binds with high affinity to nuclear components. Green et al. (1986) also cloned and sequenced human estrogen receptor cDNA, using the breast cancer cell line MCF-7. They found extensive homology between ESR cDNA and the ERBA oncogene.

Chaidarun and Alexander (1998) examined the effects of a human ESR1 isoform on estrogen-mediated gene activation in U2-OS osteosarcoma cells. ESR1-5, an ESR1 variant generated by an alternate splice event that omits exon 5 and alters the reading frame of the resulting mRNA, was coexpressed with normal ESR1 in several estrogen-responsive neoplastic tissues. ESR1-5 encodes the hormone-independent trans-activating function (AF-1), as well as the constitutive receptor dimerization and DNA-binding domains. The ESR1-5 protein is prematurely truncated and lacks the majority of the hormone-binding and activating function-2 (AF-2) domains. When ESR1-5 was cotransfected with normal ESR1, both basal and estrogen-stimulated reporter activation were increased approximately 500% over the levels observed when cells were transfected with ESR1 alone. Electromobility shift/supershift assays using nuclear extracts of U2-OS cells stably transfected with ESR1 and ESR1-5 confirmed the

constitutive binding of ESR1-5 and ESR1 protein to the estrogen-response element (ERE) sequence independent of estrogen, and also showed an increase in ESR1-5/ESR1-ERE complexes with estrogen treatment. These data were considered to be consistent with the interactive effects of normal ESR1 and ESR1-5 on transcription from classic ERE gene promoters. Chaidarun and Alexander (1998) concluded that ESR1-5 acts as a dominant-positive receptor that increases both basal and estrogen-stimulated gene transactivation of normal ESR1. Walter et al. (1985) determined that the human ESR gene maps to chromosome 6. By in situ hybridization, using a cDNA probe containing the coding sequence for the estrogen receptor, Gosden et al. (1986) assigned the gene to 6q24-q27. To localize ESR more precisely, Menasce et al. (1993) isolated a YAC containing the gene and mapped it to 6q25.1 by fluorescence in situ hybridization (FISH) and a new simple method of post-FISH chromosome banding. Using a single interspecific backcross, Justice et al. (1990) demonstrated the genetic location of the *Esr* gene in relation to other loci on mouse chromosome 10. Animal model experiments lend further support to the function of ESR1. Davis et al. (2002) noted that studies in humans and

rodent models had suggested that estrogen may provide protection against age-related cataracts. The presence of estrogen receptors in the eye indicates that estrogen protection may result from direct interactions with its receptors in the eye, instead of being an indirect consequence from effects on another tissue. Davis et al. (2002) validated the concept that estrogen is beneficial for the eye. In transgenic mice expressing ER-delta-3, a natural variant of ESR1 with an in-frame deletion of exon 3 resulting from alternative splicing, they found that cortical cataracts spontaneously formed in females after puberty and progressed with age.

[28140] It is appreciated that the abovementioned animal model for ESR1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[28141] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28142] Greene, G. L.; Gilna, P.; Waterfield, M.; Baker, A.; Hort, Y.; Shine, J. : Sequence and expression of human estrogen receptor complementary DNA. Science 231: 1150-1154, 1986. ; and

[28143] Davis, V. L.; Chan, C.-C.; Schoen, T. J.; Couse, J. F.; Chader, G. J.; Korach, K. S. : An estrogen receptor repressor induces cataract formation in transgenic mice. Proc. Nat. Acad. Sci.

[28144] Further studies establishing the function and utilities of ESR1 are found in John Hopkins OMIM database record ID 133430, and in cited publications numbered 2132–2152, 877, 3104–313 and 3444–3446 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Potassium Channel, Subfamily K, Member 4 (KCNK4, Accession NM\_016611) is another VGAM695 host target gene. KCNK4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNK4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNK4 BINDING SITE, designated SEQ ID:18717, to the nucleotide sequence of VGAM695 RNA, herein designated VGAM RNA, also designated SEQ ID:3406.

[28145] Another function of VGAM695 is therefore inhibition of Potassium Channel, Subfamily K, Member 4 (KCNK4, Accession NM\_016611). Accordingly, utilities of VGAM695

include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNK4. Neogenin Homolog 1 (chicken) (NEO1, Accession NM\_002499) is another VGAM695 host target gene. NEO1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEO1 BINDING SITE, designated SEQ ID:8319, to the nucleotide sequence of VGAM695 RNA, herein designated VGAM RNA, also designated SEQ ID:3406.

[28146] Another function of VGAM695 is therefore inhibition of Neogenin Homolog 1 (chicken) (NEO1, Accession NM\_002499), a gene which regulates the transition of undifferentiated proliferating cells to their differentiated state. Accordingly, utilities of VGAM695 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEO1. The function of NEO1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM329.HDAC9-PENDING (Accession NM\_014707) is another VGAM695 host target

gene. HDAC9–PENDING BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HDAC9–PENDING, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HDAC9–PENDING BINDING SITE, designated SEQ ID:16252, to the nucleotide sequence of VGAM695 RNA, herein designated VGAM RNA, also designated SEQ ID:3406.

[28147] Another function of VGAM695 is therefore inhibition of HDAC9–PENDING (Accession NM\_014707). Accordingly, utilities of VGAM695 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HDAC9–PENDING. KIAA1634 (Accession XM\_032749) is another VGAM695 host target gene. KIAA1634 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1634, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1634 BINDING SITE, designated SEQ ID:31754, to the nucleotide sequence of VGAM695 RNA, herein designated VGAM RNA, also designated SEQ ID:3406.



[28148] Another function of VGAM695 is therefore inhibition of KIAA1634 (Accession XM\_032749). Accordingly, utilities of VGAM695 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1634. Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession XM\_053740) is another VGAM695 host target gene. TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TP53INP1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2, designated SEQ ID:36120 and SEQ ID:27111 respectively, to the nucleotide sequence of VGAM695 RNA, herein designated VGAM RNA, also designated SEQ ID:3406.

[28149] Another function of VGAM695 is therefore inhibition of Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession XM\_053740). Accordingly, utilities of VGAM695 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TP53INP1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention,

referred to here as Viral Genomic Address Messenger 696 (VGAM696) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28150] VGAM696 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM696 was detected is described hereinabove with reference to Figs. 1–8.

[28151] VGAM696 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM696 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28152] VGAM696 gene encodes a VGAM696 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM696 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM696 precursor RNA is designated SEQ ID:682, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:682 is located at position 13163 relative to the genome of Human Coronavirus 229E.

[28153] VGAM696 precursor RNA folds onto itself, forming VGAM696 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28154] An enzyme complex designated DICER COMPLEX, `dices` the VGAM696 folded precursor RNA into VGAM696 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM696 RNA is designated SEQ ID:3407, and is provided hereinbelow with reference to the sequence listing part.

[28155] VGAM696 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM696 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM696 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28156] VGAM696 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM696 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM696 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM696 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM696 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28157] The complementary binding of VGAM696 RNA, herein designated VGAM RNA, to host target binding sites on VGAM696 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM696 host target RNA into VGAM696 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28158] It is appreciated that VGAM696 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM696 host target genes. The mRNA of each one of this plurality of VGAM696 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM696 RNA, herein designated VGAM RNA, and which when bound by VGAM696 RNA causes inhibition of translation of respective one or more VGAM696 host target proteins.

[28159] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM696 gene, herein designated VGAM GENE, on one or more VGAM696 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28160] It is yet further appreciated that a function of VGAM696 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM696 correlate with, and may be deduced from, the identity of

the host target genes which VGAM696 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28161] Nucleotide sequences of the VGAM696 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM696 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM696 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM696 are further described hereinbelow with reference to Table 1.

[28162] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM696 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM696 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28163] As mentioned hereinabove with reference to Fig. 1, a function of VGAM696 gene, herein designated VGAM is inhibition of expression of VGAM696 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM696 correlate with, and may be deduced from, the identity of the target genes which VGAM696

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28164] CGTHBA (Accession NM\_012075) is a VGAM696 host target gene. CGTHBA BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CGTHBA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CGTHBA BINDING SITE, designated SEQ ID:14361, to the nucleotide sequence of VGAM696 RNA, herein designated VGAM RNA, also designated SEQ ID:3407.

[28165] A function of VGAM696 is therefore inhibition of CGTHBA (Accession NM\_012075). Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CGTHBA. SORCS2 (Accession NM\_020777) is another VGAM696 host target gene. SORCS2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SORCS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SORCS2 BINDING SITE,



designated SEQ ID:21871, to the nucleotide sequence of VGAM696 RNA, herein designated VGAM RNA, also designated SEQ ID:3407.

[28166] Another function of VGAM696 is therefore inhibition of SORCS2 (Accession NM\_020777). Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORCS2. Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3, Accession NM\_004273) is another VGAM696 host target gene. CHST3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHST3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST3 BINDING SITE, designated SEQ ID:10478, to the nucleotide sequence of VGAM696 RNA, herein designated VGAM RNA, also designated SEQ ID:3407.

[28167] Another function of VGAM696 is therefore inhibition of Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3, Accession NM\_004273). Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHST3. KIAA0205

(Accession NM\_014873) is another VGAM696 host target gene. KIAA0205 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0205, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0205 BINDING SITE, designated SEQ ID:17004, to the nucleotide sequence of VGAM696 RNA, herein designated VGAM RNA, also designated SEQ ID:3407.

[28168] Another function of VGAM696 is therefore inhibition of KIAA0205 (Accession NM\_014873). Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0205. MIG-6 (Accession NM\_018948) is another VGAM696 host target gene. MIG-6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MIG-6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MIG-6 BINDING SITE, designated SEQ ID:21019, to the nucleotide sequence of VGAM696 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3407.

[28169] Another function of VGAM696 is therefore inhibition of MIG-6 (Accession NM\_018948). Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MIG-6. STAF65(gamma) (Accession NM\_014860) is another VGAM696 host target gene. STAF65(gamma) BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STAF65(gamma), corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAF65(gamma) BINDING SITE, designated SEQ ID:16921, to the nucleotide sequence of VGAM696 RNA, herein designated VGAM RNA, also designated SEQ ID:3407.

[28170] Another function of VGAM696 is therefore inhibition of STAF65(gamma) (Accession NM\_014860). Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAF65(gamma). LOC201685 (Accession XM\_117325) is another VGAM696 host target gene. LOC201685 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by

LOC201685, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201685 BINDING SITE, designated SEQ ID:43387, to the nucleotide sequence of VGAM696 RNA, herein designated VGAM RNA, also designated SEQ ID:3407.

[28171] Another function of VGAM696 is therefore inhibition of LOC201685 (Accession XM\_117325). Accordingly, utilities of VGAM696 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201685. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 697 (VGAM697) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28172] VGAM697 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM697 was detected is described hereinabove with reference to Figs. 1-8.

[28173] VGAM697 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Human Coronavirus 229E. VGAM697 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28174] VGAM697 gene encodes a VGAM697 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM697 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM697 precursor RNA is designated SEQ ID:683, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:683 is located at position 2149 relative to the genome of Human Coronavirus 229E.

[28175] VGAM697 precursor RNA folds onto itself, forming VGAM697 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28176] An enzyme complex designated DICER COMPLEX, `dices` the VGAM697 folded precursor RNA into VGAM697 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 68%) nucleotide sequence of VGAM697 RNA is designated SEQ ID:3408, and is provided hereinbelow with reference to the sequence listing part.

[28177] VGAM697 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM697 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM697 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28178] VGAM697 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM697 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM697 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM697 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM697 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28179] The complementary binding of VGAM697 RNA, herein designated VGAM RNA, to host target binding sites on VGAM697 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM697 host tar-

get RNA into VGAM697 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28180] It is appreciated that VGAM697 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM697 host target genes. The mRNA of each one of this plurality of VGAM697 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM697 RNA, herein designated VGAM RNA, and which when bound by VGAM697 RNA causes inhibition of translation of respective one or more VGAM697 host target proteins.

[28181] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM697 gene, herein designated VGAM GENE, on one or more VGAM697 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4



and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28182] It is yet further appreciated that a function of VGAM697 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM697 correlate with, and may be deduced from, the identity of the host target genes which VGAM697 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28183] Nucleotide sequences of the VGAM697 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM697 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM697 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM697 are further

described hereinbelow with reference to Table 1.

[28184] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM697 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM697 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28185] As mentioned hereinabove with reference to Fig. 1, a function of VGAM697 gene, herein designated VGAM is inhibition of expression of VGAM697 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM697 correlate with, and may be deduced from, the identity of the target genes which VGAM697 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28186] Epithelial Membrane Protein 1 (EMP1, Accession NM\_001423) is a VGAM697 host target gene. EMP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EMP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EMP1

BINDING SITE, designated SEQ ID:7135, to the nucleotide sequence of VGAM697 RNA, herein designated VGAM RNA, also designated SEQ ID:3408.

[28187] A function of VGAM697 is therefore inhibition of Epithelial Membrane Protein 1 (EMP1, Accession NM\_001423), a gene which plays a role in squamous cell differentiation; member of the PMP22/EMP/MP20 family of membrane glycoproteins. Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EMP1. The function of EMP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM107. McKusick-Kaufman Syndrome (MKKS, Accession NM\_018848) is another VGAM697 host target gene. MKKS BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MKKS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MKKS BINDING SITE, designated SEQ ID:20833, to the nucleotide sequence of VGAM697 RNA, herein designated VGAM RNA, also designated SEQ ID:3408.

[28188] Another function of VGAM697 is therefore inhibition of McKusick–Kaufman Syndrome (MKKS, Accession NM\_018848). Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MKKS. Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005) is another VGAM697 host target gene. PCDHA9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA9 BINDING SITE, designated SEQ ID:15211, to the nucleotide sequence of VGAM697 RNA, herein designated VGAM RNA, also designated SEQ ID:3408.

[28189] Another function of VGAM697 is therefore inhibition of Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005), a gene which is a calcium–dependent cell–adhesion protein. Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA9. The function of PCDHA9 and its association with various diseases and clinical conditions, has been established by previous studies, as de–

scribed hereinabove with reference to VGAM71. Tripartite Motif-containing 9 (TRIM9, Accession NM\_015163) is another VGAM697 host target gene. TRIM9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM9 BINDING SITE, designated SEQ ID:17512, to the nucleotide sequence of VGAM697 RNA, herein designated VGAM RNA, also designated SEQ ID:3408.

[28190] Another function of VGAM697 is therefore inhibition of Tripartite Motif-containing 9 (TRIM9, Accession NM\_015163), a gene which may function as a positive regulator for mannosylphosphate transferase and is required to mediate mannosylphosphate transfer in both the core and outer chain portions of n-linked oligosaccharides. Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM9. The function of TRIM9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74. F-box

Only Protein 21 (FBXO21, Accession NM\_033624) is another VGAM697 host target gene. FBXO21 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FBXO21, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO21 BINDING SITE, designated SEQ ID:27320, to the nucleotide sequence of VGAM697 RNA, herein designated VGAM RNA, also designated SEQ ID:3408.

[28191] Another function of VGAM697 is therefore inhibition of F-box Only Protein 21 (FBXO21, Accession NM\_033624). Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXO21. KIAA0721 (Accession XM\_171125) is another VGAM697 host target gene. KIAA0721 BINDING SITE1 and KIAA0721 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KIAA0721, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0721 BINDING SITE1 and KIAA0721 BINDING SITE2, designated SEQ ID:45927

and SEQ ID:22320 respectively, to the nucleotide sequence of VGAM697 RNA, herein designated VGAM RNA, also designated SEQ ID:3408.

[28192] Another function of VGAM697 is therefore inhibition of KIAA0721 (Accession XM\_171125). Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0721. LOC157798 (Accession XM\_098827) is another VGAM697 host target gene. LOC157798 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157798, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157798 BINDING SITE, designated SEQ ID:41849, to the nucleotide sequence of VGAM697 RNA, herein designated VGAM RNA, also designated SEQ ID:3408.

[28193] Another function of VGAM697 is therefore inhibition of LOC157798 (Accession XM\_098827). Accordingly, utilities of VGAM697 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157798. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 698 (VGAM698) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28194] VGAM698 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM698 was detected is described hereinabove with reference to Figs. 1–8.

[28195] VGAM698 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM698 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28196] VGAM698 gene encodes a VGAM698 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM698 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM698 precursor RNA is designated SEQ ID:684, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:684 is located at position 16358 relative to the genome of Hu–



man Coronavirus 229E.

[28197] VGAM698 precursor RNA folds onto itself, forming VGAM698 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28198] An enzyme complex designated DICER COMPLEX, `dices` the VGAM698 folded precursor RNA into VGAM698 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM698 RNA is designated SEQ ID:3409, and is provided hereinbelow with reference to the sequence listing part.

[28199] VGAM698 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM698 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM698 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28200] VGAM698 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM698 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM698 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM698 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM698 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28201] The complementary binding of VGAM698 RNA, herein designated VGAM RNA, to host target binding sites on VGAM698 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM698 host target RNA into VGAM698 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28202] It is appreciated that VGAM698 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM698 host target genes. The mRNA of each one of this plurality of VGAM698 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM698 RNA, herein designated VGAM RNA, and which when bound by VGAM698 RNA causes inhibition of translation of respective one or more VGAM698 host target proteins.

[28203] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM698 gene, herein designated VGAM GENE, on one or more VGAM698 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28204] It is yet further appreciated that a function of VGAM698 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM698 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM698

correlate with, and may be deduced from, the identity of the host target genes which VGAM698 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28205] Nucleotide sequences of the VGAM698 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM698 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM698 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM698 are further described hereinbelow with reference to Table 1.

[28206] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM698 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM698 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28207] As mentioned hereinabove with reference to Fig. 1, a function of VGAM698 gene, herein designated VGAM is inhibition of expression of VGAM698 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM698 correlate with, and may be deduced

from, the identity of the target genes which VGAM698 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28208] DKFZp547M072 (Accession XM\_028067) is a VGAM698 host target gene. DKFZp547M072 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp547M072, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547M072 BINDING SITE, designated SEQ ID:30614, to the nucleotide sequence of VGAM698 RNA, herein designated VGAM RNA, also designated SEQ ID:3409.

[28209] A function of VGAM698 is therefore inhibition of DKFZp547M072 (Accession XM\_028067). Accordingly, utilities of VGAM698 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547M072. KIAA1130 (Accession XM\_031104) is another VGAM698 host target gene. KIAA1130 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1130, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1130 BINDING SITE, designated SEQ ID:31285, to the nucleotide sequence of VGAM698 RNA, herein designated VGAM RNA, also designated SEQ ID:3409.

[28210] Another function of VGAM698 is therefore inhibition of KIAA1130 (Accession XM\_031104). Accordingly, utilities of VGAM698 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1130. p25 (Accession NM\_007030) is another VGAM698 host target gene. p25 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by p25, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of p25 BINDING SITE, designated SEQ ID:13893, to the nucleotide sequence of VGAM698 RNA, herein designated VGAM RNA, also designated SEQ ID:3409.

[28211] Another function of VGAM698 is therefore inhibition of p25 (Accession NM\_007030). Accordingly, utilities of VGAM698 include diagnosis, prevention and treatment of diseases and clinical conditions associated with p25. LOC144501 (Accession XM\_096612) is another VGAM698

host target gene. LOC144501 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144501, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144501 BINDING SITE, designated SEQ ID:40426, to the nucleotide sequence of VGAM698 RNA, herein designated VGAM RNA, also designated SEQ ID:3409.

[28212] Another function of VGAM698 is therefore inhibition of LOC144501 (Accession XM\_096612). Accordingly, utilities of VGAM698 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144501. LOC150333 (Accession XM\_097874) is another VGAM698 host target gene. LOC150333 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150333 BINDING SITE, designated SEQ ID:41198, to the nucleotide sequence of VGAM698 RNA, herein designated VGAM RNA, also designated SEQ ID:3409.



[28213] Another function of VGAM698 is therefore inhibition of LOC150333 (Accession XM\_097874). Accordingly, utilities of VGAM698 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150333. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 699 (VGAM699) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28214] VGAM699 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM699 was detected is described hereinabove with reference to Figs. 1–8.

[28215] VGAM699 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM699 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28216] VGAM699 gene encodes a VGAM699 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM699

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM699 precursor RNA is designated SEQ ID:685, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:685 is located at position 2991 relative to the genome of Human Coronavirus 229E.

[28217] VGAM699 precursor RNA folds onto itself, forming VGAM699 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28218] An enzyme complex designated DICER COMPLEX, `dices` the VGAM699 folded precursor RNA into VGAM699 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 48%) nucleotide sequence of VGAM699 RNA is designated SEQ ID:3410, and is provided hereinbelow with reference to the sequence listing part.

[28219] VGAM699 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM699 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM699 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[28220] VGAM699 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM699 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM699 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM699 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM699 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28221] The complementary binding of VGAM699 RNA, herein designated VGAM RNA, to host target binding sites on VGAM699 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM699 host target RNA into VGAM699 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28222] It is appreciated that VGAM699 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM699 host target genes. The mRNA of each one of this plurality of VGAM699 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM699 RNA, herein designated VGAM RNA, and which when bound by VGAM699 RNA causes inhibition of translation of respective one or more VGAM699 host target proteins.

[28223] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM699 gene, herein designated VGAM GENE, on one or more VGAM699 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28224] It is yet further appreciated that a function of VGAM699 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM699 correlate with, and may be deduced from, the identity of the host target genes which VGAM699 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28225] Nucleotide sequences of the VGAM699 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM699 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM699 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM699 are further described hereinbelow with reference to Table 1.

[28226] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM699 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM699 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[28227] As mentioned hereinabove with reference to Fig. 1, a function of VGAM699 gene, herein designated VGAM is inhibition of expression of VGAM699 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM699 correlate with, and may be deduced from, the identity of the target genes which VGAM699 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28228] Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III) (AGL, Accession NM\_000646) is a VGAM699 host target gene. AGL BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by AGL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AGL BINDING SITE, designated SEQ ID:6302, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28229] A function of VGAM699 is therefore inhibition of Amylo-1, 6-glucosidase, 4-alpha-glucanotransferase (glycogen debranching enzyme, glycogen storage disease type III)

(AGL, Accession NM\_000646). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AGL. ATPase, Class I, Type 8B, Member 2 (ATP8B2, Accession XM\_036933) is another VGAM699 host target gene.

ATP8B2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP8B2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP8B2 BINDING SITE, designated SEQ ID:32510, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28230] Another function of VGAM699 is therefore inhibition of ATPase, Class I, Type 8B, Member 2 (ATP8B2, Accession XM\_036933). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP8B2. Cholinergic Receptor, Nicotinic, Beta Polypeptide 2 (neuronal) (CHRNA2, Accession NM\_000748) is another VGAM699 host target gene. CHRNA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by



CHRNA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHRNA2 BINDING SITE, designated SEQ ID:6400, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28231] Another function of VGAM699 is therefore inhibition of Cholinergic Receptor, Nicotinic, Beta Polypeptide 2 (neuronal) (CHRNA2, Accession NM\_000748), a gene which mediates fast signal transmission at synapses. Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHRNA2. The function of CHRNA2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM166. Paired Box Gene 9 (PAX9, Accession NM\_006194) is another VGAM699 host target gene. PAX9 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PAX9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of PAX9 BINDING SITE, designated SEQ ID:12866, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28232] Another function of VGAM699 is therefore inhibition of Paired Box Gene 9 (PAX9, Accession NM\_006194), a gene which is a key regulator during the development of a wide range of organ hypodontia. Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAX9. The function of PAX9 has been established by previous studies. Stockton et al. (2000) identified a frameshift mutation within the paired domain of PAX9, following genomewide analysis of a family segregating autosomal dominant oligodontia (OMIM Ref. No. 604625). Affected members had normal primary dentition but lacked most permanent molars. In addition to lack of permanent molars, some individuals also lacked maxillary and/or mandibular second premolars, as well as mandibular central incisors. Stockton et al. (2000) first performed a genomewide search using microsatellite markers and identified a critical region that included the PAX9 gene on chromosome 14. Mutation analysis of the coding regions of exons 2–4 of PAX9

demonstrated an insertion of a G at nucleotide 219, resulting in frameshift. Relative to the finding of other abnormalities in PAX9 knockout mice, Stockton et al. (2000) noted that affected members of this family showed no limb anomalies and no evidence for calcium metabolism abnormalities or compromised immune system.

Oligodontia is defined as agenesis of 6 or more permanent teeth without associated systemic disorders, and hypodontia as absence of less than 6 teeth. The incidence of familial tooth agenesis varies with each class of teeth.

Most commonly affected are third molars ('wisdom teeth'), followed by either upper lateral incisors or lower second premolars; agenesis involving first and second molars is very rare. The homeo box gene MSX1 (OMIM Ref. No. 142983) was found to be mutant in a single family with agenesis of the second premolars and third molars. Animal model experiments lend further support to the function of PAX9. Peters et al. (1998) generated Pax9-deficient mice and showed that PAX9 is essential for the development of a variety of organs and skeletal elements. Homozygous Pax9 mutant mice died shortly after birth, most likely as a consequence of a cleft secondary palate. Homozygous knockout mice lacked a thymus, parathyroid

glands, and ultimobranchial bodies, organs which are derived from the pharyngeal pouches. In all limbs, a supernumerary preaxial digit was formed, but the flexor of the hindlimb toes was missing. Furthermore, craniofacial and visceral skeletogenesis was disturbed, and all teeth were absent. In Pax9-deficient embryos, tooth development was arrested at the bud stage. At that stage, Pax9 is required for the mesenchymal expression of Bmp4, Msx1, and Lef1, suggesting a role for Pax9 in the establishment of the inductive capacity of the tooth mesenchyme.

[28233] It is appreciated that the abovementioned animal model for PAX9 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[28234] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28235] Stockton, D. W.; Das, P.; Goldenberg, M.; D'Souza, R. N.; Patel, P. I. : Mutation of PAX9 is associated with oligodontia. (Letter) Nature Genet. 24: 18–19, 2000. ; and

[28236] Peters, H.; Neubuser, A.; Kratochwil, K.; Balling, R. : Pax9-deficient mice lack pharyngeal pouch derivatives and teeth and exhibit craniofacial and limb abnormalities.

Genes Dev. 12: 2.

[28237] Further studies establishing the function and utilities of PAX9 are found in John Hopkins OMIM database record ID 167416, and in cited publications numbered 10949–10952, 1071 and 10953–10954 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tumor Necrosis Factor (ligand) Superfamily, Member 8 (TNFSF8, Accession NM\_001244) is another VGAM699 host target gene. TNFSF8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFSF8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFSF8 BINDING SITE, designated SEQ ID:6913, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28238] Another function of VGAM699 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 8 (TNFSF8, Accession NM\_001244), a gene which cytokine that binds to tnfrsf8/cd30. induces proliferation of t cells. Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with TNFSF8. The function of TNFSF8 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM655. Tetratricopeptide Repeat Domain 3 (TTC3, Accession NM\_003316) is another VGAM699 host target gene. TTC3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TTC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TTC3 BINDING SITE, designated SEQ ID:9313, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28239] Another function of VGAM699 is therefore inhibition of Tetratricopeptide Repeat Domain 3 (TTC3, Accession NM\_003316), a gene which contains tetratricopeptide repeat (TPR) motifs. Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TTC3. The function of TTC3 has been established by previous studies. The Down syndrome (DS; 190685) region on chromosome 21, which is responsible for the main features of DS, has been de-

fined by analysis of DS patients with partial trisomy 21. Within the DS region, Ohira et al. (1996) constructed a 1.6-Mb P1 contig map on 21q22.2 and performed cDNA library screening and exon trapping using these P1 clones and a human fetal brain cDNA library. They obtained 67 cDNA fragments and 52 possible exons. Among them, 23 cDNA fragments and 4 exons were derived from a single gene by localization on P1 clones and by Northern analysis. To obtain the full-length cDNA sequence, longer cDNA clones were further screened from another human cDNA library that was enriched with longer cDNA species. These clones were assembled to a sequence of 9,045 bp. The cDNA encodes a 2,025-amino acid protein containing 3 tetratricopeptide repeat (TPR) motifs (amino acid residues 231–264, 265–298, and 299–332). The authors symbolized the gene TPRD for a gene containing the TPR motifs on the Down syndrome region. The TPR domain has been found in protein phosphatases and in other proteins involved in the regulation of RNA synthesis or mitosis. Independently, Tsukahara et al. (1996) identified and cloned a 9,078-bp cDNA, which they designated TPRDI, from the Down syndrome critical region by exon trapping. The cDNA encodes a putative protein (TPRDI) of 2,025

amino acid residues. Two isoforms, TPRDII (8,992 bp) and TPRDIII (7,416 bp), were also isolated. TPRDII, which is probably an alternative splicing product from the TPRD gene transcript, encodes 2 large open reading frames of 200 and 1,792 amino acid residues, respectively. TPRDIII, which is probably generated by transcription from an alternative start site of the TPRD gene, encodes a putative protein of 1,715 amino acid residues. Northern blot analysis revealed that TPRDI and its isoforms are present in 7- to 17-day mouse embryos and in all the human adult and fetal tissues examined. TPRDI has 3 units of the 34-amino acid TPR motif, which may mediate interaction with various proteins. A larger open reading frame encoded by TPRDII also has 3 units of the TPR motif, but TPRDIII has only two-thirds of this motif unit. Thus, the TPRD gene may belong to the TPR gene family. Near-central and C-terminal regions of TPRDs showed some homology to several matrix proteins such as trichohyalin and bullous pemphigoid antigen. The authors speculated that overexpression of the TPRD gene may cause several morphologic anomalies observed in Down syndrome.

[28240] Full details of the abovementioned studies are described in the following publications, the disclosure of which are



hereby incorporated by reference:

- [28241] Ohira, M.; Ootsuyama A.; Suzuki, E.; Ichikawa, H.; Seki, N.; Nagase, T.; Monura, N.; Ohki, M. : Identification of a novel human gene containing the tetratricopeptide repeat domain from the Down syndrome region of chromosome 21. DNA Res. 3: 9–16, 1996. ; and
- [28242] Tsukahara, F.; Hattori, M.; Muraki, T.; Sakaki, Y. : Identification and cloning of a novel cDNA belonging to tetratricopeptide repeat gene family from Down syndrome-critical region 21q22.2.
- [28243] Further studies establishing the function and utilities of TTC3 are found in John Hopkins OMIM database record ID 602259, and in cited publications numbered 931–932 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ATP-binding Cassette, Sub-family A (ABC1), Member 10 (ABCA10, Accession NM\_080282) is another VGAM699 host target gene. ABCA10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABCA10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCA10 BINDING SITE, designated SEQ

ID:27824, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28244] Another function of VGAM699 is therefore inhibition of ATP-binding Cassette, Sub-family A (ABC1), Member 10 (ABCA10, Accession NM\_080282). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCA10. ADMP (Accession NM\_145035) is another VGAM699 host target gene. ADMP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADMP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADMP BINDING SITE, designated SEQ ID:29654, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28245] Another function of VGAM699 is therefore inhibition of ADMP (Accession NM\_145035). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADMP. AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Acces-

sion NM\_080551) is another VGAM699 host target gene. AP1GBP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AP1GBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP1GBP1 BINDING SITE, designated SEQ ID:27876, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28246] Another function of VGAM699 is therefore inhibition of AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Accession NM\_080551). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP1GBP1. Chloride Intracellular Channel 2 (CLIC2, Accession NM\_001289) is another VGAM699 host target gene. CLIC2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CLIC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLIC2 BINDING SITE, designated SEQ ID:6965, to the nucleotide se-

quence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28247] Another function of VGAM699 is therefore inhibition of Chloride Intracellular Channel 2 (CLIC2, Accession NM\_001289). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLIC2. FLJ10246 (Accession NM\_018038) is another VGAM699 host target gene. FLJ10246 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10246, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10246 BINDING SITE, designated SEQ ID:19783, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28248] Another function of VGAM699 is therefore inhibition of FLJ10246 (Accession NM\_018038). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10246. FLJ10701 (Accession NM\_018183) is another VGAM699 host target gene. FLJ10701 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ10701, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10701 BINDING SITE, designated SEQ ID:20023, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28249] Another function of VGAM699 is therefore inhibition of FLJ10701 (Accession NM\_018183). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10701. FLJ14297 (Accession NM\_024903) is another VGAM699 host target gene. FLJ14297 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14297, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14297 BINDING SITE, designated SEQ ID:24390, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28250] Another function of VGAM699 is therefore inhibition of

FLJ14297 (Accession NM\_024903). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14297. FLJ20618 (Accession NM\_017903) is another VGAM699 host target gene. FLJ20618 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20618, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20618 BINDING SITE, designated SEQ ID:19568, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28251] Another function of VGAM699 is therefore inhibition of FLJ20618 (Accession NM\_017903). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20618. Keratin, Hair, Basic, 2 (KRTHB2, Accession NM\_033033) is another VGAM699 host target gene. KRTHB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KRTHB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of KRTHB2 BINDING SITE, designated SEQ ID:26923, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28252] Another function of VGAM699 is therefore inhibition of Keratin, Hair, Basic, 2 (KRTHB2, Accession NM\_033033). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KRTHB2. MGC21675 (Accession NM\_052861) is another VGAM699 host target gene. MGC21675 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC21675, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC21675 BINDING SITE, designated SEQ ID:27443, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28253] Another function of VGAM699 is therefore inhibition of MGC21675 (Accession NM\_052861). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

MGC21675. Squamous Cell Carcinoma Antigen Recognised By T Cells 3 (SART3, Accession NM\_014706) is another VGAM699 host target gene. SART3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SART3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SART3 BINDING SITE, designated SEQ ID:16249, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28254] Another function of VGAM699 is therefore inhibition of Squamous Cell Carcinoma Antigen Recognised By T Cells 3 (SART3, Accession NM\_014706). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SART3. Ubiquitin-like, Containing PHD and RING Finger Domains, 2 (UHRF2, Accession XM\_055929) is another VGAM699 host target gene. UHRF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UHRF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of UHRF2 BINDING SITE, designated SEQ ID:36354, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28255] Another function of VGAM699 is therefore inhibition of Ubiquitin-like, Containing PHD and RING Finger Domains, 2 (UHRF2, Accession XM\_055929). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UHRF2. LOC147093 (Accession XM\_097184) is another VGAM699 host target gene. LOC147093 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147093, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147093 BINDING SITE, designated SEQ ID:40799, to the nucleotide sequence of VGAM699 RNA, herein designated VGAM RNA, also designated SEQ ID:3410.

[28256] Another function of VGAM699 is therefore inhibition of LOC147093 (Accession XM\_097184). Accordingly, utilities of VGAM699 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC147093. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 700 (VGAM700) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28257] VGAM700 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM700 was detected is described hereinabove with reference to Figs. 1–8.

[28258] VGAM700 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM700 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28259] VGAM700 gene encodes a VGAM700 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM700 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM700 precursor RNA is designated SEQ ID:686, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:686 is located at position 5282 relative to the genome of Human Coronavirus 229E.

[28260] VGAM700 precursor RNA folds onto itself, forming VGAM700 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28261] An enzyme complex designated DICER COMPLEX, `dices` the VGAM700 folded precursor RNA into VGAM700 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM700 RNA is designated SEQ ID:3411, and is provided hereinbelow with reference to the sequence listing part.

[28262] VGAM700 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM700 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM700 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28263] VGAM700 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM700 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM700 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM700 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM700 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[28264] The complementary binding of VGAM700 RNA, herein designated VGAM RNA, to host target binding sites on VGAM700 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM700 host target RNA into VGAM700 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28265] It is appreciated that VGAM700 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM700 host target genes. The mRNA of each one of this plurality of VGAM700 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM700 RNA, herein designated VGAM RNA, and which when bound by VGAM700 RNA causes in-

hibition of translation of respective one or more VGAM700 host target proteins.

[28266] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM700 gene, herein designated VGAM GENE, on one or more VGAM700 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28267] It is yet further appreciated that a function of VGAM700 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM700 include diagnosis, prevention and

treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM700 correlate with, and may be deduced from, the identity of the host target genes which VGAM700 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [28268] Nucleotide sequences of the VGAM700 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM700 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM700 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM700 are further described hereinbelow with reference to Table 1.
- [28269] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM700 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM700 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [28270] As mentioned hereinabove with reference to Fig. 1, a function of VGAM700 gene, herein designated VGAM is inhibition of expression of VGAM700 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM700 correlate with, and may be deduced from, the identity of the target genes which VGAM700 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28271] Splicing Factor, Arginine/serine-rich 2, Interacting Protein (SFRS2IP, Accession NM\_004719) is a VGAM700 host target gene. SFRS2IP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRS2IP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRS2IP BINDING SITE, designated SEQ ID:11083, to the nucleotide sequence of VGAM700 RNA, herein designated VGAM RNA, also designated SEQ ID:3411.

[28272] A function of VGAM700 is therefore inhibition of Splicing Factor, Arginine/serine-rich 2, Interacting Protein (SFRS2IP, Accession NM\_004719), a gene which plays an essential role in pre-mRNA splicing. Accordingly, utilities of VGAM700 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRS2IP. The function of SFRS2IP has been established by



previous studies. Like other SR proteins, the SC35 (OMIM Ref. No. 600813) splicing factor contains an arginine/serine-rich (RS) domain and an RNA-binding motif. Using a yeast 2-hybrid screen with SC35 as bait, Zhang and Wu (1998) isolated a HeLa cell partial cDNA encoding SIP1, a novel SC35-interacting protein. They used the partial cDNA to screen a HeLa cell library and recovered cDNAs corresponding to the entire SIP1 coding region. The predicted 1,403-amino acid protein contains an RS domain similar to those found in several SR proteins and a region of weak similarity to the *Drosophila* splicing regulator suppressor of white-apricot (SWAP; 601945). In addition, the C-terminal region of SIP1 contains an RNA polymerase II C-terminal domain (CTD)-binding motif. Although the predicted molecular mass of SIP1 is 158 kD, the protein migrates at 210 kD by SDS-PAGE. The authors suggested that this discrepancy might result from posttranslational modifications such as phosphorylation, which is known to cause aberrant migration of several RS domain-containing proteins in SDS-PAGE. Yeast 2-hybrid assays and immunoprecipitation studies showed that SIP1 interacts with several SR proteins as well as with U2AF65 (OMIM Ref. No. 191318) and U1-70K (OMIM Ref. No. 180740), proteins

associated with the 3-prime and 5-prime splice sites, respectively. Antibodies against SIP1 depleted splicing activity from a HeLa cell nuclear extract. In the SIP1-depleted nuclear extracts, the authors found that the formation of prespliceosomal complexes A and B was deficient. Zhang and Wu (1998) concluded that SIP1 is a novel RS domain protein required for pre-mRNA splicing. By performing a yeast 2-hybrid assay to identify proteins that interact with CTD, Tanner et al. (1997) isolated partial cDNAs encoding SIP1, which they called CTD-associated SR protein 11 (OMIM Ref. No. CASP11) or SR-related protein of 129 kD (SRrp129). Northern blot analysis detected expression of the approximately 6-kb SRrp129 mRNA in all tissues tested.

[28273] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28274] Zhang, W.-J.; Wu, J. Y. : Sip1, a novel RS domain-containing protein essential for pre-mRNA splicing. *Molec. Cell. Biol.* 18: 676-684, 1998. ; and

[28275] Tanner, S.; Stagljar, I.; Georgiev, O.; Schaffner, W.; Bourquin, J.-P. : A novel SR-related protein specifically interacts with the carboxy-terminal domain (CTD) of RNA

polymerase II through.

[28276] Further studies establishing the function and utilities of SFRS2IP are found in John Hopkins OMIM database record ID 603668, and in cited publications numbered 992–993 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ21477 (Accession NM\_025153) is another VGAM700 host target gene. FLJ21477 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ21477, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21477 BINDING SITE, designated SEQ ID:24791, to the nucleotide sequence of VGAM700 RNA, herein designated VGAM RNA, also designated SEQ ID:3411.

[28277] Another function of VGAM700 is therefore inhibition of FLJ21477 (Accession NM\_025153). Accordingly, utilities of VGAM700 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21477. LOC220477 (Accession XM\_071675) is another VGAM700 host target gene. LOC220477 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of

mRNA encoded by LOC220477, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220477 BINDING SITE, designated SEQ ID:37410, to the nucleotide sequence of VGAM700 RNA, herein designated VGAM RNA, also designated SEQ ID:3411.

[28278] Another function of VGAM700 is therefore inhibition of LOC220477 (Accession XM\_071675). Accordingly, utilities of VGAM700 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220477. LOC255147 (Accession XM\_171024) is another VGAM700 host target gene. LOC255147 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255147, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255147 BINDING SITE, designated SEQ ID:45803, to the nucleotide sequence of VGAM700 RNA, herein designated VGAM RNA, also designated SEQ ID:3411.

[28279] Another function of VGAM700 is therefore inhibition of LOC255147 (Accession XM\_171024). Accordingly, utilities

of VGAM700 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255147. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 701 (VGAM701) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28280] VGAM701 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM701 was detected is described hereinabove with reference to Figs. 1–8.

[28281] VGAM701 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM701 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28282] VGAM701 gene encodes a VGAM701 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM701 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM701 precursor RNA is designated SEQ ID:687, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:687 is located at position 21134 relative to the genome of Human Coronavirus 229E.

[28283] VGAM701 precursor RNA folds onto itself, forming VGAM701 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28284] An enzyme complex designated DICER COMPLEX, `dices` the VGAM701 folded precursor RNA into VGAM701 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM701 RNA is designated SEQ ID:3412, and

is provided hereinbelow with reference to the sequence listing part.

[28285] VGAM701 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM701 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM701 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28286] VGAM701 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM701 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM701 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM701 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM701 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28287] The complementary binding of VGAM701 RNA, herein designated VGAM RNA, to host target binding sites on VGAM701 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM701 host target RNA into VGAM701 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28288] It is appreciated that VGAM701 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM701 host target genes. The mRNA of each one of this plurality of VGAM701 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-



plementary to VGAM701 RNA, herein designated VGAM RNA, and which when bound by VGAM701 RNA causes inhibition of translation of respective one or more VGAM701 host target proteins.

[28289] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM701 gene, herein designated VGAM GENE, on one or more VGAM701 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28290] It is yet further appreciated that a function of VGAM701 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM701 correlate with, and may be deduced from, the identity of the host target genes which VGAM701 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28291] Nucleotide sequences of the VGAM701 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM701 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM701 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM701 are further described hereinbelow with reference to Table 1.

[28292] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM701 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM701 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28293] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM701 gene, herein designated VGAM is inhibition of expression of VGAM701 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM701 correlate with, and may be deduced from, the identity of the target genes which VGAM701 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28294] Chromosome 20 Open Reading Frame 45 (C20orf45, Accession NM\_016045) is a VGAM701 host target gene. C20orf45 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf45, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf45 BINDING SITE, designated SEQ ID:18120, to the nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA, also designated SEQ ID:3412.

[28295] A function of VGAM701 is therefore inhibition of Chromosome 20 Open Reading Frame 45 (C20orf45, Accession NM\_016045). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf45. FLJ22060

(Accession NM\_024612) is another VGAM701 host target gene. FLJ22060 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22060, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22060 BINDING SITE, designated SEQ ID:23865, to the nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA, also designated SEQ ID:3412.

[28296] Another function of VGAM701 is therefore inhibition of FLJ22060 (Accession NM\_024612). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22060. LOC130507 (Accession XM\_059440) is another VGAM701 host target gene. LOC130507 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130507, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130507 BINDING SITE, designated SEQ ID:36996, to the nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA,

also designated SEQ ID:3412.

[28297] Another function of VGAM701 is therefore inhibition of LOC130507 (Accession XM\_059440). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130507. LOC152185 (Accession NM\_144718) is another VGAM701 host target gene. LOC152185 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152185, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152185 BINDING SITE, designated SEQ ID:29538, to the nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA, also designated SEQ ID:3412.

[28298] Another function of VGAM701 is therefore inhibition of LOC152185 (Accession NM\_144718). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152185. LOC154089 (Accession XM\_087846) is another VGAM701 host target gene. LOC154089 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154089, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154089 BINDING SITE, designated SEQ ID:39462, to the nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA, also designated SEQ ID:3412.

[28299] Another function of VGAM701 is therefore inhibition of LOC154089 (Accession XM\_087846). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154089. LOC203411 (Accession XM\_117547) is another VGAM701 host target gene. LOC203411 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203411, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203411 BINDING SITE, designated SEQ ID:43564, to the nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA, also designated SEQ ID:3412.

[28300] Another function of VGAM701 is therefore inhibition of LOC203411 (Accession XM\_117547). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC203411. LOC51634 (Accession NM\_016024) is another VGAM701 host target gene. LOC51634 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51634, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51634 BINDING SITE, designated SEQ ID:18104, to the nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA, also designated SEQ ID:3412.

[28301] Another function of VGAM701 is therefore inhibition of LOC51634 (Accession NM\_016024). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51634. LOC91923 (Accession XM\_041526) is another VGAM701 host target gene. LOC91923 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91923 BINDING SITE, designated SEQ ID:33542, to the

nucleotide sequence of VGAM701 RNA, herein designated VGAM RNA, also designated SEQ ID:3412.

[28302] Another function of VGAM701 is therefore inhibition of LOC91923 (Accession XM\_041526). Accordingly, utilities of VGAM701 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91923. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 702 (VGAM702) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28303] VGAM702 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM702 was detected is described hereinabove with reference to Figs. 1–8.

[28304] VGAM702 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM702 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28305] VGAM702 gene encodes a VGAM702 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM702 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM702 precursor RNA is designated SEQ ID:688, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:688 is located at position 22902 relative to the genome of Human Coronavirus 229E.

[28306] VGAM702 precursor RNA folds onto itself, forming VGAM702 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28307] An enzyme complex designated DICER COMPLEX, `dices` the VGAM702 folded precursor RNA into VGAM702 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM702 RNA is designated SEQ ID:3413, and is provided hereinbelow with reference to the sequence listing part.

[28308] VGAM702 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM702 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM702 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28309] VGAM702 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM702 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM702 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM702 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM702 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28310] The complementary binding of VGAM702 RNA, herein designated VGAM RNA, to host target binding sites on VGAM702 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM702 host target RNA into VGAM702 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28311] It is appreciated that VGAM702 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM702 host target genes. The mRNA of each one of this plurality of VGAM702 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM702 RNA, herein designated VGAM RNA, and which when bound by VGAM702 RNA causes inhibition of translation of respective one or more VGAM702 host target proteins.

[28312] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM702 gene, herein designated VGAM GENE, on one or more VGAM702 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[28313] It is yet further appreciated that a function of VGAM702 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM702 correlate with, and may be deduced from, the identity of the host target genes which VGAM702 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28314] Nucleotide sequences of the VGAM702 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM702 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM702 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM702 are further described hereinbelow with reference to Table 1.

[28315] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM702 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM702 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28316] As mentioned hereinabove with reference to Fig. 1, a function of VGAM702 gene, herein designated VGAM is inhibition of expression of VGAM702 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM702 correlate with, and may be deduced from, the identity of the target genes which VGAM702 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28317] Splicing Factor, Arginine/serine-rich 2, Interacting Protein (SFRS2IP, Accession NM\_004719) is a VGAM702 host target gene. SFRS2IP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRS2IP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRS2IP BINDING SITE, designated SEQ ID:11082, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28318] A function of VGAM702 is therefore inhibition of Splicing

Factor, Arginine/serine-rich 2, Interacting Protein (SFRS2IP, Accession NM\_004719), a gene which plays an essential role in pre-mRNA splicing. Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRS2IP. The function of SFRS2IP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM700. FLJ13456 (Accession XM\_038291) is another VGAM702 host target gene. FLJ13456 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13456, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13456 BINDING SITE, designated SEQ ID:32795, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28319] Another function of VGAM702 is therefore inhibition of FLJ13456 (Accession XM\_038291). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13456. FLJ21276 (Accession NM\_024633) is another VGAM702

host target gene. FLJ21276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21276 BINDING SITE, designated SEQ ID:23903, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28320] Another function of VGAM702 is therefore inhibition of FLJ21276 (Accession NM\_024633). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21276. KIAA0940 (Accession NM\_014912) is another VGAM702 host target gene. KIAA0940 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0940, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0940 BINDING SITE, designated SEQ ID:17149, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.



[28321] Another function of VGAM702 is therefore inhibition of KIAA0940 (Accession NM\_014912). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0940. KIAA1363 (Accession XM\_045056) is another VGAM702 host target gene. KIAA1363 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1363, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1363 BINDING SITE, designated SEQ ID:34330, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28322] Another function of VGAM702 is therefore inhibition of KIAA1363 (Accession XM\_045056). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1363. Keratin, Hair, Basic, 5 (KRTHB5, Accession NM\_002283) is another VGAM702 host target gene. KRTHB5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KRTHB5, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KRTHB5 BINDING SITE, designated SEQ ID:8065, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28323] Another function of VGAM702 is therefore inhibition of Keratin, Hair, Basic, 5 (KRTHB5, Accession NM\_002283). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KRTHB5. MGC12466 (Accession NM\_033213) is another VGAM702 host target gene. MGC12466 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC12466, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC12466 BINDING SITE, designated SEQ ID:27065, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28324] Another function of VGAM702 is therefore inhibition of MGC12466 (Accession NM\_033213). Accordingly, utilities

of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC12466. Protocadherin 17 (PCDH17, Accession NM\_014459) is another VGAM702 host target gene. PCDH17 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PCDH17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDH17 BINDING SITE, designated SEQ ID:15813, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28325] Another function of VGAM702 is therefore inhibition of Protocadherin 17 (PCDH17, Accession NM\_014459). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH17. UBA2 (Accession NM\_005499) is another VGAM702 host target gene. UBA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of UBA2 BINDING SITE, designated SEQ ID:12002, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28326] Another function of VGAM702 is therefore inhibition of UBA2 (Accession NM\_005499). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBA2. LOC88523 (Accession NM\_033111) is another VGAM702 host target gene. LOC88523 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC88523, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC88523 BINDING SITE, designated SEQ ID:26960, to the nucleotide sequence of VGAM702 RNA, herein designated VGAM RNA, also designated SEQ ID:3413.

[28327] Another function of VGAM702 is therefore inhibition of LOC88523 (Accession NM\_033111). Accordingly, utilities of VGAM702 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC88523. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 703 (VGAM703) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28328] VGAM703 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM703 was detected is described hereinabove with reference to Figs. 1–8.

[28329] VGAM703 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM703 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28330] VGAM703 gene encodes a VGAM703 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM703 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM703 precursor RNA is designated SEQ ID:689, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:689 is

located at position 22503 relative to the genome of Human Coronavirus 229E.

[28331] VGAM703 precursor RNA folds onto itself, forming VGAM703 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28332] An enzyme complex designated DICER COMPLEX, `dices` the VGAM703 folded precursor RNA into VGAM703 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM703 RNA is designated SEQ ID:3414, and is provided hereinbelow with reference to the sequence listing part.

[28333] VGAM703 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM703 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM703 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[28334] VGAM703 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM703 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM703 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM703 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM703 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[28335] The complementary binding of VGAM703 RNA, herein designated VGAM RNA, to host target binding sites on VGAM703 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM703 host target RNA into VGAM703 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28336] It is appreciated that VGAM703 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM703 host target genes. The mRNA of each one of this plurality of VGAM703 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM703 RNA, herein designated VGAM RNA, and which when bound by VGAM703 RNA causes inhibition of translation of respective one or more VGAM703



host target proteins.

[28337] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM703 gene, herein designated VGAM GENE, on one or more VGAM703 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28338] It is yet further appreciated that a function of VGAM703 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM703 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E.

Specific functions, and accordingly utilities, of VGAM703 correlate with, and may be deduced from, the identity of the host target genes which VGAM703 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28339] Nucleotide sequences of the VGAM703 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM703 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM703 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM703 are further described hereinbelow with reference to Table 1.

[28340] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM703 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM703 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28341] As mentioned hereinabove with reference to Fig. 1, a function of VGAM703 gene, herein designated VGAM is inhibition of expression of VGAM703 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM703 correlate with, and may be deduced from, the identity of the target genes which VGAM703 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28342] Chloride Channel 6 (CLCN6, Accession NM\_001286) is a VGAM703 host target gene. CLCN6 BINDING SITE1 through CLCN6 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CLCN6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLCN6 BINDING SITE1 through CLCN6 BINDING SITE3, designated SEQ ID:6958, SEQ ID:22335 and SEQ ID:22340 respectively, to the nucleotide sequence of VGAM703 RNA, herein designated VGAM RNA, also designated SEQ ID:3414.

[28343] A function of VGAM703 is therefore inhibition of Chloride Channel 6 (CLCN6, Accession NM\_001286), a gene which is a voltage-gated chloride channel. Accordingly, utilities of VGAM703 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCN6. The function of CLCN6 and its association with various diseases and clinical conditions, has been established by

previous studies, as described hereinabove with reference to VGAM599.LOC150951 (Accession XM\_097975) is another VGAM703 host target gene. LOC150951 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150951, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150951 BINDING SITE, designated SEQ ID:41275, to the nucleotide sequence of VGAM703 RNA, herein designated VGAM RNA, also designated SEQ ID:3414.

[28344] Another function of VGAM703 is therefore inhibition of LOC150951 (Accession XM\_097975). Accordingly, utilities of VGAM703 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150951. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 704 (VGAM704) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28345] VGAM704 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM704 was detected is described hereinabove with reference to Figs. 1–8.

[28346] VGAM704 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM704 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28347] VGAM704 gene encodes a VGAM704 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM704 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM704 precursor RNA is designated SEQ ID:690, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:690 is located at position 21569 relative to the genome of Human Coronavirus 229E.

[28348] VGAM704 precursor RNA folds onto itself, forming VGAM704 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28349] An enzyme complex designated DICER COMPLEX, `dices` the VGAM704 folded precursor RNA into VGAM704 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 54%) nucleotide sequence of VGAM704 RNA is designated SEQ ID:3415, and is provided hereinbelow with reference to the sequence listing part.

[28350] VGAM704 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM704 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM704 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28351] VGAM704 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM704 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM704 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM704 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM704 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28352] The complementary binding of VGAM704 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM704 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM704 host target RNA into VGAM704 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28353] It is appreciated that VGAM704 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM704 host target genes. The mRNA of each one of this plurality of VGAM704 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM704 RNA, herein designated VGAM RNA, and which when bound by VGAM704 RNA causes inhibition of translation of respective one or more VGAM704 host target proteins.

[28354] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM704 gene, herein designated VGAM GENE, on one or more VGAM704 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other



known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28355] It is yet further appreciated that a function of VGAM704 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM704 correlate with, and may be deduced from, the identity of the host target genes which VGAM704 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28356] Nucleotide sequences of the VGAM704 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

5' duced 5' VGAM704 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM704 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM704 are further described hereinbelow with reference to Table 1.

[28357] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM704 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM704 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28358] As mentioned hereinabove with reference to Fig. 1, a function of VGAM704 gene, herein designated VGAM is inhibition of expression of VGAM704 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM704 correlate with, and may be deduced from, the identity of the target genes which VGAM704 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28359] Interleukin 1 Receptor, Type I (IL1R1, Accession NM\_000877) is a VGAM704 host target gene. IL1R1 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by IL1R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL1R1 BINDING SITE, designated SEQ ID:6561, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28360] A function of VGAM704 is therefore inhibition of Interleukin 1 Receptor, Type I (IL1R1, Accession NM\_000877), a gene which is a receptor for interleukin-1 alpha (il-1a), beta (il-1b), and interleukin-1 receptor antagonist protein (il-1ra). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL1R1. The function of IL1R1 has been established by previous studies. Interleukin-1, which has a role as a mediator in inflammation, actually consists of 2 separate but related proteins, IL1-alpha (OMIM Ref. No. 147720) and IL1-beta (OMIM Ref. No. 147760). Dower et al. (1986) showed that the cell surface receptors for the 2 forms of interleukin-1 are identical. Sims et al. (1989) cloned the human IL1R gene and compared it with the mouse gene. Both contain a single membrane-spanning segment, a large cytoplasmic region, and an extracellular,

IL1-binding portion composed of 3 immunoglobulin-like domains. The IL1R gene expressed in human dermal fibroblasts was found to be identical to that expressed in T cells. By a combination of somatic cell hybrid analysis and chromosomal in situ hybridization, Copeland et al. (1991) mapped the IL1R gene to human chromosome 2q12. By RFLP analysis in interspecific backcrosses, Copeland et al. (1991) mapped the corresponding mouse gene at the centromeric end of chromosome 1, a region homologous to a portion of human chromosome 2

[28361] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28362] Dower, S. K.; Kronheim, S. R.; Hopp, T. P.; Cantrell, M.; Deeley, M.; Gillis, S.; Henney, C. S.; Urdal, D. L. : The cell surface receptors for interleukin-1(alpha) and interleukin-1(beta) are identical. *Nature* 324: 266-268, 1986. ; and

[28363] Sims, J. E.; Acres, R. B.; Grubin, C. E.; McMahan, C. J.; Wignall, J. M.; March, C. J.; Dower, S. K. : Cloning the interleukin 1 receptor from human T cells. *Proc. Nat. Acad. Sci.* 86: 89.

[28364] Further studies establishing the function and utilities of IL1R1 are found in John Hopkins OMIM database record ID

147810, and in cited publications numbered 3041–3044 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphodiesterase 4D, CAMP-specific (phosphodiesterase E3 duncce homolog, *Drosophila*) (PDE4D, Accession XM\_056815) is another VGAM704 host target gene. PDE4D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDE4D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDE4D BINDING SITE, designated SEQ ID:36430, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28365] Another function of VGAM704 is therefore inhibition of Phosphodiesterase 4D, CAMP-specific (phosphodiesterase E3 duncce homolog, *Drosophila*) (PDE4D, Accession XM\_056815), a gene which has similarity to *Drosophila* dnc, which is the affected protein in learning and memory mutant duncce. Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDE4D. The function of PDE4D and its association with various diseases and clinical

cal conditions, has been established by previous studies, as described hereinabove with reference to VGAM180.Sarcoma Amplified Sequence (SAS, Accession NM\_005981) is another VGAM704 host target gene. SAS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SAS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SAS BINDING SITE, designated SEQ ID:12605, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28366] Another function of VGAM704 is therefore inhibition of Sarcoma Amplified Sequence (SAS, Accession NM\_005981), a gene which is a member of the transmembrane 4 superfamily (TM4SF) and may be involved in growth-related cellular processes T. Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SAS. The function of SAS has been established by previous studies. SAS is a member of the transmembrane 4 superfamily, all members of which have 4 hydrophobic domains. This family includes various tumor-associated

antigens such as CO-029 (OMIM Ref. No. 600769), L6 (M3S1; 191155), and ME491 (CD63; 155740), hematopoietic cell antigens such as CD9 (OMIM Ref. No. 143030), CD53 (OMIM Ref. No. 151525), CD37 (OMIM Ref. No. 151523), and TAPA1 (OMIM Ref. No. 186845), as well as the parasitic trematode surface proteins Sm23 and Sj23. Meltzer et al. (1991) identified and partially cloned a gene that is amplified in human malignant fibrous histiocytoma. They demonstrated that the gene, designated sarcoma amplified sequence, is located on chromosome 12 by hybridization to a rodent/human somatic cell hybrid mapping panel. They further regionalized the assignment to 12q13-q14 by fluorescence in situ hybridization. This chromosomal region is commonly involved in rearrangements in myxoid liposarcoma, benign lipoma, and uterine leiomyoma. Meltzer et al. (1991) identified SAS amplification in 5 of 29 malignant fibrous histiocytoma biopsies, 4 of 12 liposarcoma biopsies, and 1 osteogenic sarcoma cell line. Since amplification of cellular oncogenes occurs frequently in human cancers, identification of amplified genes in tumor cells is a useful approach for understanding genetic alterations. Jankowski et al. (1995) characterized the genomic structure of SAS and showed that it has

6 exons spanning approximately 3.2 kb.

[28367] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28368] Jankowski, S. A.; De Jong, P.; Meltzer, P. S. : Genomic structure of SAS, a member of the transmembrane 4 superfamily amplified in human sarcomas. *Genomics* 25: 501–506, 1995. ; and

[28369] Meltzer, P. S.; Jankowski, S. A.; Dal Cin, P.; Sandberg, A. A.; Paz, I. B.; Coccia, M. A.; Smith, S. H. : Identification and cloning of a novel amplified DNA sequence in human malignant.

[28370] Further studies establishing the function and utilities of SAS are found in John Hopkins OMIM database record ID 181035, and in cited publications numbered 5704–5705 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transcription Factor 7 (T-cell specific, HMG-box) (TCF7, Accession NM\_003202) is another VGAM704 host target gene. TCF7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TCF7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-



trates the complementarity of the nucleotide sequences of TCF7 BINDING SITE, designated SEQ ID:9190, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28371] Another function of VGAM704 is therefore inhibition of Transcription Factor 7 (T-cell specific, HMG-box) (TCF7, Accession NM\_003202). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCF7. Adaptor-related Protein Complex 3, Mu 2 Subunit (AP3M2, Accession NM\_006803) is another VGAM704 host target gene.

AP3M2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AP3M2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP3M2 BINDING SITE, designated SEQ ID:13675, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28372] Another function of VGAM704 is therefore inhibition of Adaptor-related Protein Complex 3, Mu 2 Subunit (AP3M2, Accession NM\_006803). Accordingly, utilities of

VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP3M2. DKFZP564I1171 (Accession XM\_049568) is another VGAM704 host target gene. DKFZP564I1171 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP564I1171, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564I1171 BINDING SITE, designated SEQ ID:35444, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28373] Another function of VGAM704 is therefore inhibition of DKFZP564I1171 (Accession XM\_049568). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564I1171. KIAA0433 (Accession NM\_015216) is another VGAM704 host target gene. KIAA0433 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0433, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA0433 BINDING SITE, designated SEQ ID:17547, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28374] Another function of VGAM704 is therefore inhibition of KIAA0433 (Accession NM\_015216). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0433. KIAA0557 (Accession XM\_085507) is another VGAM704 host target gene. KIAA0557 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0557, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0557 BINDING SITE, designated SEQ ID:38206, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28375] Another function of VGAM704 is therefore inhibition of KIAA0557 (Accession XM\_085507). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0557. KIAA1350 (Accession XM\_052597) is another VGAM704 host target gene. KIAA1350 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1350 BINDING SITE, designated SEQ ID:36000, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28376] Another function of VGAM704 is therefore inhibition of KIAA1350 (Accession XM\_052597). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1350. KIAA1557 (Accession XM\_028289) is another VGAM704 host target gene. KIAA1557 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1557, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1557 BINDING SITE, designated SEQ ID:30640, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28377] Another function of VGAM704 is therefore inhibition of

KIAA1557 (Accession XM\_028289). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1557. KIAA1735 (Accession XM\_113686) is another VGAM704 host target gene. KIAA1735 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1735, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1735 BINDING SITE, designated SEQ ID:42345, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28378] Another function of VGAM704 is therefore inhibition of KIAA1735 (Accession XM\_113686). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1735. MGC5466 (Accession XM\_054436) is another VGAM704 host target gene. MGC5466 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC5466, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of MGC5466 BINDING SITE, designated SEQ ID:36158, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28379] Another function of VGAM704 is therefore inhibition of MGC5466 (Accession XM\_054436). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5466. Retinoic Acid Induced 17 (RAI17, Accession XM\_166091) is another VGAM704 host target gene. RAI17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAI17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAI17 BINDING SITE, designated SEQ ID:43861, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28380] Another function of VGAM704 is therefore inhibition of Retinoic Acid Induced 17 (RAI17, Accession XM\_166091). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAI17. Spi-B Transcription Factor

(Spi-1/PU.1 related) (SPIB, Accession NM\_003121) is another VGAM704 host target gene. SPIB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPIB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPIB BINDING SITE, designated SEQ ID:9092, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28381] Another function of VGAM704 is therefore inhibition of Spi-B Transcription Factor (Spi-1/PU.1 related) (SPIB, Accession NM\_003121). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPIB. Sperm Specific Antigen 2 (SSFA2, Accession XM\_057458) is another VGAM704 host target gene. SSFA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSFA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSFA2 BINDING SITE, designated SEQ ID:36514, to the nucleotide sequence of

VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28382] Another function of VGAM704 is therefore inhibition of Sperm Specific Antigen 2 (SSFA2, Accession XM\_057458). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSFA2. SSH-3 (Accession NM\_017857) is another VGAM704 host target gene. SSH-3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSH-3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSH-3 BINDING SITE, designated SEQ ID:19535, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28383] Another function of VGAM704 is therefore inhibition of SSH-3 (Accession NM\_017857). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSH-3. LOC153474 (Accession XM\_087684) is another VGAM704 host target gene. LOC153474 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of



mRNA encoded by LOC153474, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153474 BINDING SITE, designated SEQ ID:39380, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28384] Another function of VGAM704 is therefore inhibition of LOC153474 (Accession XM\_087684). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153474. LOC200734 (Accession XM\_114286) is another VGAM704 host target gene. LOC200734 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200734, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200734 BINDING SITE, designated SEQ ID:42839, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28385] Another function of VGAM704 is therefore inhibition of LOC200734 (Accession XM\_114286). Accordingly, utilities

of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200734. LOC202347 (Accession XM\_117390) is another VGAM704 host target gene. LOC202347 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC202347, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202347 BINDING SITE, designated SEQ ID:43429, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28386] Another function of VGAM704 is therefore inhibition of LOC202347 (Accession XM\_117390). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202347. LOC89919 (Accession XM\_027244) is another VGAM704 host target gene. LOC89919 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC89919, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC89919 BINDING SITE, designated SEQ ID:30463, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28387] Another function of VGAM704 is therefore inhibition of LOC89919 (Accession XM\_027244). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC89919. LOC93550 (Accession XM\_051999) is another VGAM704 host target gene. LOC93550 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93550, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93550 BINDING SITE, designated SEQ ID:35930, to the nucleotide sequence of VGAM704 RNA, herein designated VGAM RNA, also designated SEQ ID:3415.

[28388] Another function of VGAM704 is therefore inhibition of LOC93550 (Accession XM\_051999). Accordingly, utilities of VGAM704 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93550. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 705 (VGAM705) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28389] VGAM705 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM705 was detected is described hereinabove with reference to Figs. 1–8.

[28390] VGAM705 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM705 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28391] VGAM705 gene encodes a VGAM705 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM705 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM705 precursor RNA is designated SEQ ID:691, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:691 is located at position 23467 relative to the genome of Hu–

man Coronavirus 229E.

[28392] VGAM705 precursor RNA folds onto itself, forming VGAM705 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28393] An enzyme complex designated DICER COMPLEX, `dices` the VGAM705 folded precursor RNA into VGAM705 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM705 RNA is designated SEQ ID:3416, and is provided hereinbelow with reference to the sequence listing part.

[28394] VGAM705 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM705 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM705 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28395] VGAM705 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM705 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM705 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM705 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM705 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28396] The complementary binding of VGAM705 RNA, herein designated VGAM RNA, to host target binding sites on VGAM705 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM705 host target RNA into VGAM705 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28397] It is appreciated that VGAM705 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM705 host target genes. The mRNA of each one of this plurality of VGAM705 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM705 RNA, herein designated VGAM RNA, and which when bound by VGAM705 RNA causes inhibition of translation of respective one or more VGAM705 host target proteins.

[28398] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM705 gene, herein designated VGAM GENE, on one or more VGAM705 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28399] It is yet further appreciated that a function of VGAM705 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM705



correlate with, and may be deduced from, the identity of the host target genes which VGAM705 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28400] Nucleotide sequences of the VGAM705 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM705 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM705 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM705 are further described hereinbelow with reference to Table 1.

[28401] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM705 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM705 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28402] As mentioned hereinabove with reference to Fig. 1, a function of VGAM705 gene, herein designated VGAM is inhibition of expression of VGAM705 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM705 correlate with, and may be deduced

from, the identity of the target genes which VGAM705 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28403] Aldehyde Dehydrogenase 1 Family, Member A3 (ALDH1A3, Accession NM\_000693) is a VGAM705 host target gene. ALDH1A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALDH1A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALDH1A3 BINDING SITE, designated SEQ ID:6351, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28404] A function of VGAM705 is therefore inhibition of Aldehyde Dehydrogenase 1 Family, Member A3 (ALDH1A3, Accession NM\_000693), a gene which plays a major role in the detoxification of aldehydes generated by alcohol metabolism and lipid peroxidation. Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALDH1A3. The function of ALDH1A3 and its association with various diseases and clinical conditions, has been es-

established by previous studies, as described hereinabove with reference to VGAM565. Chromosome 9 Open Reading Frame 9 (C9orf9, Accession NM\_018956) is another VGAM705 host target gene. C9orf9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C9orf9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C9orf9 BINDING SITE, designated SEQ ID:21025, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28405] Another function of VGAM705 is therefore inhibition of Chromosome 9 Open Reading Frame 9 (C9orf9, Accession NM\_018956). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C9orf9. DKFZP727C091 (Accession XM\_038689) is another VGAM705 host target gene. DKFZP727C091 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP727C091, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of DKFZP727C091 BINDING SITE, designated SEQ ID:32909, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28406] Another function of VGAM705 is therefore inhibition of DKFZP727C091 (Accession XM\_038689). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP727C091. Endothelial Cell-specific Molecule 1 (ESM1, Accession NM\_007036) is another VGAM705 host target gene. ESM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESM1 BINDING SITE, designated SEQ ID:13916, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28407] Another function of VGAM705 is therefore inhibition of Endothelial Cell-specific Molecule 1 (ESM1, Accession NM\_007036). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with ESM1. F-box Only Protein 4 (FBXO4, Accession NM\_033484) is another VGAM705 host target gene. FBXO4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FBXO4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO4 BINDING SITE, designated SEQ ID:27263, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28408] Another function of VGAM705 is therefore inhibition of F-box Only Protein 4 (FBXO4, Accession NM\_033484). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXO4. FLJ11273 (Accession NM\_018374) is another VGAM705 host target gene. FLJ11273 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11273, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11273 BINDING SITE, designated SEQ ID:20396, to the

nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28409] Another function of VGAM705 is therefore inhibition of FLJ11273 (Accession NM\_018374). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11273. FLJ21916 (Accession NM\_023112) is another VGAM705 host target gene. FLJ21916 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21916, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21916 BINDING SITE, designated SEQ ID:23382, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28410] Another function of VGAM705 is therefore inhibition of FLJ21916 (Accession NM\_023112). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21916. Lipoma HMGIC Fusion Partner-like 2 (LHFPL2, Accession XM\_046054) is another VGAM705 host target gene. LHFPL2 BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by LHFPL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LHFPL2 BINDING SITE, designated SEQ ID:34662, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28411] Another function of VGAM705 is therefore inhibition of Lipoma HMGIC Fusion Partner-like 2 (LHFPL2, Accession XM\_046054). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LHFPL2. Seizure Related 6 Homolog (mouse) (SEZ6, Accession XM\_058869) is another VGAM705 host target gene. SEZ6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SEZ6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEZ6 BINDING SITE, designated SEQ ID:36776, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28412] Another function of VGAM705 is therefore inhibition of Seizure Related 6 Homolog (mouse) (SEZ6, Accession XM\_058869). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEZ6. Sialyltransferase 8C (alpha2,3Galbeta1,4GlcNAcalpha 2,8-sialyltransferase) (SIAT8C, Accession NM\_015879) is another VGAM705 host target gene. SIAT8C BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SIAT8C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIAT8C BINDING SITE, designated SEQ ID:18028, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28413] Another function of VGAM705 is therefore inhibition of Sialyltransferase 8C (alpha2,3Galbeta1,4GlcNAcalpha 2,8-sialyltransferase) (SIAT8C, Accession NM\_015879). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIAT8C. LOC163255 (Accession XM\_092121) is another VGAM705 host target gene.



LOC163255 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163255 BINDING SITE, designated SEQ ID:40107, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28414] Another function of VGAM705 is therefore inhibition of LOC163255 (Accession XM\_092121). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163255. LOC164397 (Accession XM\_092780) is another VGAM705 host target gene. LOC164397 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC164397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164397 BINDING SITE, designated SEQ ID:40149, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28415] Another function of VGAM705 is therefore inhibition of LOC164397 (Accession XM\_092780). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC164397. LOC255862 (Accession XM\_170505) is another VGAM705 host target gene. LOC255862 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255862, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255862 BINDING SITE, designated SEQ ID:45341, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28416] Another function of VGAM705 is therefore inhibition of LOC255862 (Accession XM\_170505). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255862. LOC256176 (Accession XM\_172889) is another VGAM705 host target gene. LOC256176 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256176, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256176 BINDING SITE, designated SEQ ID:46171, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28417] Another function of VGAM705 is therefore inhibition of LOC256176 (Accession XM\_172889). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256176. LOC91050 (Accession XM\_035703) is another VGAM705 host target gene. LOC91050 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91050, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91050 BINDING SITE, designated SEQ ID:32338, to the nucleotide sequence of VGAM705 RNA, herein designated VGAM RNA, also designated SEQ ID:3416.

[28418] Another function of VGAM705 is therefore inhibition of LOC91050 (Accession XM\_035703). Accordingly, utilities of VGAM705 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC91050. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 706 (VGAM706) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28419] VGAM706 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM706 was detected is described hereinabove with reference to Figs. 1–8.

[28420] VGAM706 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Coronavirus 229E. VGAM706 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28421] VGAM706 gene encodes a VGAM706 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM706 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM706 precursor RNA is designated SEQ ID:692, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:692 is located at position 23583 relative to the genome of Human Coronavirus 229E.

[28422] VGAM706 precursor RNA folds onto itself, forming VGAM706 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28423] An enzyme complex designated DICER COMPLEX, `dices` the VGAM706 folded precursor RNA into VGAM706 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM706 RNA is designated SEQ ID:3417, and is provided hereinbelow with reference to the sequence listing part.

[28424] VGAM706 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM706 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM706 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28425] VGAM706 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM706 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM706 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM706 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM706 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[28426] The complementary binding of VGAM706 RNA, herein designated VGAM RNA, to host target binding sites on VGAM706 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM706 host target RNA into VGAM706 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28427] It is appreciated that VGAM706 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM706 host target genes. The mRNA of each one of this plurality of VGAM706 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM706 RNA, herein designated VGAM RNA, and which when bound by VGAM706 RNA causes in-

hibition of translation of respective one or more VGAM706 host target proteins.

[28428] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM706 gene, herein designated VGAM GENE, on one or more VGAM706 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28429] It is yet further appreciated that a function of VGAM706 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM706 include diagnosis, prevention and



treatment of viral infection by Human Coronavirus 229E. Specific functions, and accordingly utilities, of VGAM706 correlate with, and may be deduced from, the identity of the host target genes which VGAM706 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [28430] Nucleotide sequences of the VGAM706 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM706 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM706 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM706 are further described hereinbelow with reference to Table 1.
- [28431] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM706 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM706 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [28432] As mentioned hereinabove with reference to Fig. 1, a function of VGAM706 gene, herein designated VGAM is inhibition of expression of VGAM706 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM706 correlate with, and may be deduced from, the identity of the target genes which VGAM706 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28433] A Disintegrin and Metalloproteinase Domain 10 (ADAM10, Accession NM\_001110) is a VGAM706 host target gene. ADAM10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAM10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM10 BINDING SITE, designated SEQ ID:6769, to the nucleotide sequence of VGAM706 RNA, herein designated VGAM RNA, also designated SEQ ID:3417.

[28434] A function of VGAM706 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 10 (ADAM10, Accession NM\_001110), a gene which Member of ADAM family of zinc metalloproteases. Accordingly, utilities of VGAM706 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM10. The function of ADAM10 has been established by previous

studies. Wolfsberg et al. (1995) identified a family of proteins containing a disintegrin and metalloproteinase (ADAM) domain. Members of this family are cell surface proteins with a unique structure possessing both potential adhesion and protease domains. Tumor necrosis factor- $\alpha$  (TNFA; 191160) is synthesized as a proinflammatory cytokine from a 233-amino acid precursor. Conversion of the membrane-bound precursor to a secreted mature protein is mediated by a protease termed TNFA convertase. Lunn et al. (1997) found that ADAM10 possesses TNFA convertase activity. TNFA is involved in a variety of diseases. To elucidate whether the ADAM10 locus maps to the same region as a disease susceptibility, Yamazaki et al. (1997) mapped the ADAM10 locus. Using a radiation hybrid mapping method, they showed that ADAM10 is located on 15q21.3-q23. Although ephrins form a high-affinity multivalent complex with their receptors present on axons, axons can be rapidly repelled rather than being bound. Hattori et al. (2000) showed that ephrin-A2 (OMIM Ref. No. 602756) forms a stable complex with the metalloproteinase Kuzbanian (OMIM Ref. No. ADAM10) involving interactions outside the cleavage region and the protease domain. Eph receptor binding triggered ephrin-A2

cleavage in a localized reaction specific to the cognate ligand. The cleavage-inhibiting mutation in ephrin-A2 delayed axon withdrawal. Hattori et al. (2000) concluded that their studies reveal mechanisms for protease recognition and control of cell surface proteins, and, for ephrin-A2, they may provide a means for efficient axon detachment and termination of signaling.

[28435] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28436] Lunn, C. A.; Fan, X.; Dalie, B.; Miller, K.; Zavodny, P. J.; Narula, S. K.; Lundell, D. : Purification of ADAM 10 from bovine spleen as a TNFalpha convertase. FEBS Lett. 400: 333-335, 1997. ; and

[28437] Hattori, M.; Osterfield, M.; Flanagan, J. G. : Regulated cleavage of a contact-mediated axon repellent. Science 289: 1360-1365, 2000.

[28438] Further studies establishing the function and utilities of ADAM10 are found in John Hopkins OMIM database record ID 602192, and in cited publications numbered 1267 and 5852-5853 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger, Imprinted 2 (ZIM2, Accession NM\_015363) is another

VGAM706 host target gene. ZIM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZIM2 BINDING SITE, designated SEQ ID:17664, to the nucleotide sequence of VGAM706 RNA, herein designated VGAM RNA, also designated SEQ ID:3417.

[28439] Another function of VGAM706 is therefore inhibition of Zinc Finger, Imprinted 2 (ZIM2, Accession NM\_015363). Accordingly, utilities of VGAM706 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZIM2. LOC221715 (Accession XM\_168092) is another VGAM706 host target gene. LOC221715 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221715, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221715 BINDING SITE, designated SEQ ID:45018, to the nucleotide sequence of VGAM706 RNA, herein designated VGAM RNA, also designated SEQ ID:3417.

[28440] Another function of VGAM706 is therefore inhibition of LOC221715 (Accession XM\_168092). Accordingly, utilities of VGAM706 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221715. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 707 (VGAM707) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28441] VGAM707 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM707 was detected is described hereinabove with reference to Figs. 1–8.

[28442] VGAM707 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Invertebrate Iridescent Virus 6. VGAM707 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28443] VGAM707 gene encodes a VGAM707 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM707

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM707 precursor RNA is designated SEQ ID:693, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:693 is located at position 129865 relative to the genome of Invertebrate Iridescent Virus 6.

[28444] VGAM707 precursor RNA folds onto itself, forming VGAM707 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28445] An enzyme complex designated DICER COMPLEX, `dices` the VGAM707 folded precursor RNA into VGAM707 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 84%) nucleotide sequence of VGAM707 RNA is designated SEQ ID:3418, and is provided hereinbelow with reference to the sequence listing part.

[28446] VGAM707 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM707 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM707 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28447] VGAM707 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM707 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM707 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the



number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM707 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM707 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28448] The complementary binding of VGAM707 RNA, herein designated VGAM RNA, to host target binding sites on VGAM707 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM707 host target RNA into VGAM707 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28449] It is appreciated that VGAM707 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM707 host target genes. The mRNA of each one of this plurality of VGAM707 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM707 RNA, herein designated VGAM RNA, and which when bound by VGAM707 RNA causes inhibition of translation of respective one or more VGAM707 host target proteins.

[28450] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM707 gene, herein designated VGAM GENE, on one or more VGAM707 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28451] It is yet further appreciated that a function of VGAM707 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM707 include diagnosis, prevention and treatment of viral infection by Invertebrate Iridescent Virus 6. Specific functions, and accordingly utilities, of VGAM707 correlate with, and may be deduced from, the identity of the host target genes which VGAM707 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28452] Nucleotide sequences of the VGAM707 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM707 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM707 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM707 are further described hereinbelow with reference to Table 1.

[28453] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM707 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM707 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[28454] As mentioned hereinabove with reference to Fig. 1, a function of VGAM707 gene, herein designated VGAM is inhibition of expression of VGAM707 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM707 correlate with, and may be deduced from, the identity of the target genes which VGAM707 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28455] Eyes Absent Homolog 4 (Drosophila) (EYA4, Accession NM\_004100) is a VGAM707 host target gene. EYA4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EYA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EYA4 BINDING SITE, designated SEQ ID:10308, to the nucleotide sequence of VGAM707 RNA, herein designated VGAM RNA, also designated SEQ ID:3418.

[28456] A function of VGAM707 is therefore inhibition of Eyes Absent Homolog 4 (Drosophila) (EYA4, Accession NM\_004100), a gene which may be involved in development of the eye (by similarity). Accordingly, utilities of

VGAM707 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EYA4. The function of EYA4 has been established by previous studies. Borsani et al. (1999) presented the detailed characterization of a fourth vertebrate gene, designated EYA4, that is homologous to 'eyes absent' (eya), a key regulator of ocular development in *Drosophila*. See also EYA1 (OMIM Ref. No. 601653), EYA2 (OMIM Ref. No. 601654), and EYA3 (OMIM Ref. No. 601655). The authors found that EYA4 encodes a 640-amino acid protein containing a highly conserved C-terminal domain of 271 amino acids. In *Drosophila*, eya is known to mediate developmentally important protein-protein interactions. By radiation hybrid analysis and fluorescence in situ hybridization, Borsani et al. (1999) mapped the human EYA4 gene to 6q23. They also detected linkage, with a lod score of greater than 3, to previously mapped reference markers. They genetically mapped the mouse Eya4 gene to chromosome 10 in the vicinity of Aco2 (OMIM Ref. No. 100850), in a region homologous to human chromosome 6q22-q23. In the developing mouse embryo, Eya4 was expressed primarily in the craniofacial mesenchyme, the dermamyotome, and the limb. On the basis of map position and expression pat-

tern, EYA4 was considered a candidate for oculodentodigital dysplasia (OMIM Ref. No. 164200), but Borsani et al. (1999) found no EYA4 mutations in a panel of patients with this disorder. Wayne et al. (2001) identified mutations in the EYA4 gene that were responsible for postlingual, progressive, autosomal dominant hearing loss at the DFNA10 locus (OMIM Ref. No. 601316). Just as EYA proteins interact with members of the SIX (OMIM Ref. No. 601205) and DACH (OMIM Ref. No. 603803) protein families during early embryonic development, the authors suggested that EYA4 is also important postdevelopmentally for continued function of the mature organ of Corti.

[28457] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28458] Borsani, G.; DeGrandi, A.; Ballabio, A.; Bulfone, A.; Bernard, L.; Banfi, S.; Gattuso, C.; Mariani, M.; Dixon, M.; Donnai, D.; Metcalfe, K.; Winter, R.; Robertson, M.; Axton, R.; Brown, A.; van Heyningen, V.; Hanson, I. : EYA4, a novel vertebrate gene related to *Drosophila* eyes absent. Hum. Molec. Genet. 8: 11-23, 1999. ; and

[28459] Wayne, S.; Robertson, N. G.; DeClau, F.; Chen, N.; Verhoeven, K.; Prasad, S.; Tranebjarg, L.; Morton, C. C.; Ryan, A.

F.; Van Camp, G.; Smith, R. J. H. : Mutations in the transcriptiona.

[28460] Further studies establishing the function and utilities of EYA4 are found in John Hopkins OMIM database record ID 603550, and in cited publications numbered 494 and 9384 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. C20orf180 (Accession NM\_018431) is another VGAM707 host target gene. C20orf180 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf180, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf180 BINDING SITE, designated SEQ ID:20496, to the nucleotide sequence of VGAM707 RNA, herein designated VGAM RNA, also designated SEQ ID:3418.

[28461] Another function of VGAM707 is therefore inhibition of C20orf180 (Accession NM\_018431). Accordingly, utilities of VGAM707 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf180. LOC145474 (Accession XM\_085147) is another VGAM707 host target gene. LOC145474 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145474, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145474 BINDING SITE, designated SEQ ID:37870, to the nucleotide sequence of VGAM707 RNA, herein designated VGAM RNA, also designated SEQ ID:3418.

[28462] Another function of VGAM707 is therefore inhibition of LOC145474 (Accession XM\_085147). Accordingly, utilities of VGAM707 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145474. LOC146229 (Accession XM\_085387) is another VGAM707 host target gene. LOC146229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146229 BINDING SITE, designated SEQ ID:38112, to the nucleotide sequence of VGAM707 RNA, herein designated VGAM RNA, also designated SEQ ID:3418.

[28463] Another function of VGAM707 is therefore inhibition of



LOC146229 (Accession XM\_085387). Accordingly, utilities of VGAM707 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146229. LOC158382 (Accession XM\_098931) is another VGAM707 host target gene. LOC158382 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158382, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158382 BINDING SITE, designated SEQ ID:41967, to the nucleotide sequence of VGAM707 RNA, herein designated VGAM RNA, also designated SEQ ID:3418.

[28464] Another function of VGAM707 is therefore inhibition of LOC158382 (Accession XM\_098931). Accordingly, utilities of VGAM707 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158382. LOC163255 (Accession XM\_092121) is another VGAM707 host target gene. LOC163255 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC163255 BINDING SITE, designated SEQ ID:40108, to the nucleotide sequence of VGAM707 RNA, herein designated VGAM RNA, also designated SEQ ID:3418.

[28465] Another function of VGAM707 is therefore inhibition of LOC163255 (Accession XM\_092121). Accordingly, utilities of VGAM707 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163255. LOC200420 (Accession NM\_145300) is another VGAM707 host target gene. LOC200420 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200420 BINDING SITE, designated SEQ ID:29813, to the nucleotide sequence of VGAM707 RNA, herein designated VGAM RNA, also designated SEQ ID:3418.

[28466] Another function of VGAM707 is therefore inhibition of LOC200420 (Accession NM\_145300). Accordingly, utilities of VGAM707 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200420. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 708 (VGAM708) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28467] VGAM708 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM708 was detected is described hereinabove with reference to Figs. 1–8.

[28468] VGAM708 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Potato Virus V. VGAM708 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28469] VGAM708 gene encodes a VGAM708 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM708 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM708 precursor RNA is designated SEQ ID:694, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:694 is

located at position 9696 relative to the genome of Potato Virus V.

[28470] VGAM708 precursor RNA folds onto itself, forming VGAM708 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28471] An enzyme complex designated DICER COMPLEX, `dices` the VGAM708 folded precursor RNA into VGAM708 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 73%) nucleotide sequence of VGAM708 RNA is designated SEQ ID:3419, and is provided hereinbelow with reference to the sequence listing part.

[28472] VGAM708 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM708 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM708 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[28473] VGAM708 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM708 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM708 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM708 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM708 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[28474] The complementary binding of VGAM708 RNA, herein designated VGAM RNA, to host target binding sites on VGAM708 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM708 host target RNA into VGAM708 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28475] It is appreciated that VGAM708 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM708 host target genes. The mRNA of each one of this plurality of VGAM708 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM708 RNA, herein designated VGAM RNA, and which when bound by VGAM708 RNA causes inhibition of translation of respective one or more VGAM708

host target proteins.

[28476] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM708 gene, herein designated VGAM GENE, on one or more VGAM708 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28477] It is yet further appreciated that a function of VGAM708 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of viral infection by Potato Virus V. Specific

functions, and accordingly utilities, of VGAM708 correlate with, and may be deduced from, the identity of the host target genes which VGAM708 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28478] Nucleotide sequences of the VGAM708 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM708 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM708 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM708 are further described hereinbelow with reference to Table 1.

[28479] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM708 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM708 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28480] As mentioned hereinabove with reference to Fig. 1, a function of VGAM708 gene, herein designated VGAM is inhibition of expression of VGAM708 target genes. It is appreciated that specific functions, and accordingly utili-



ties, of VGAM708 correlate with, and may be deduced from, the identity of the target genes which VGAM708 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28481] ATPase, Cu<sup>++</sup> Transporting, Beta Polypeptide (Wilson disease) (ATP7B, Accession NM\_000053) is a VGAM708 host target gene. ATP7B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP7B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP7B BINDING SITE, designated SEQ ID:5509, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28482] A function of VGAM708 is therefore inhibition of ATPase, Cu<sup>++</sup> Transporting, Beta Polypeptide (Wilson disease) (ATP7B, Accession NM\_000053). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP7B. Egl Nine Homolog 2 (C. elegans) (EGLN2, Accession NM\_017555) is another VGAM708 host target gene. EGLN2 BINDING SITE is HOST TARGET binding site found

in the 3` untranslated region of mRNA encoded by EGLN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGLN2 BINDING SITE, designated SEQ ID:18990, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28483] Another function of VGAM708 is therefore inhibition of Egl Nine Homolog 2 (*C. elegans*) (EGLN2, Accession NM\_017555), a gene which is an essential component of the pathway. Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN2. The function of EGLN2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM432.NADH Dehydrogenase (ubiquinone) 1 Alpha Subcomplex, 5, 13kDa (NDUFA5, Accession NM\_005000) is another VGAM708 host target gene. NDUFA5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NDUFA5, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDUFA5 BINDING SITE, designated SEQ ID:11443, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28484] Another function of VGAM708 is therefore inhibition of NADH Dehydrogenase (ubiquinone) 1 Alpha Subcomplex, 5, 13kDa (NDUFA5, Accession NM\_005000), a gene which transfers electrons from nadh to the respiratory chain. Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDUFA5. The function of NDUFA5 has been established by previous studies. The multisubunit NADH:ubiquinone oxidoreductase (complex I) is the first enzyme complex in the electron transport chain of mitochondria. The iron-sulfur protein (IP) fraction of complex I is made up of 7 subunits, including B13. See NDUFS1 (OMIM Ref. No. 157655). By a combination of EST database screening and PCR, Pata et al. (1997) isolated cDNAs encoding the human homolog of bovine B13. The deduced 116-amino acid human protein has a calculated molecular weight of approximately 13 kD. Human and bovine B13 are 87% identical on the amino acid level.

Northern blot analysis revealed that the 1.6-kb B13 mRNA was expressed in all human tissues tested, with the highest levels in heart, skeletal muscle, and brain. Two additional smaller transcripts were also detected. Using Southern blots, Pata et al. (1997) determined that B13 is part of a multigene family in humans. During the course of a physical mapping project on 11p15.5, Russell et al. (1997) identified sequence with a high degree of similarity to the bovine NADH:ubiquinone oxidoreductase subunit B13. Following up on this lead, they isolated a clone with nucleotide sequence 88% and 83% identical over the predicted open reading frame with bovine and rat B13 subunit genes, respectively. The position of the initiation and termination codons was conserved. To determine the chromosomal localization of the B13 subunit gene, they screened a monochromosome somatic cell hybrid panel and showed that only the hybrid containing human chromosome 7 was positive.

[28485] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28486] Pata, I.; Tensing, K.; Metspalu, A. : A human cDNA encoding the homologue of NADH:ubiquinone oxidoreductase

subunit B13. Biochim. Biophys. Acta 1350: 115–118, 1997. ; and

[28487] Russell, M. W.; du Manoir, S.; Collins, F. S.; Brody, L. C. : Cloning of the human NADH:ubiquinone oxidoreductase subunit B13: localization to chromosome 7q32 and identification of a ps.

[28488] Further studies establishing the function and utilities of NDUFA5 are found in John Hopkins OMIM database record ID 601677, and in cited publications numbered 6195–6196 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Syntaxin Binding Protein 1 (STXBP1, Accession NM\_003165) is another VGAM708 host target gene. STXBP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by STXBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STXBP1 BINDING SITE, designated SEQ ID:9142, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28489] Another function of VGAM708 is therefore inhibition of Syntaxin Binding Protein 1 (STXBP1, Accession

NM\_003165), a gene which may play a role in determining the specificity of intracellular fusion reactions. Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STXBP1. The function of STXBP1 has been established by previous studies. Within the secretory pathway, proteins and other cargo are transferred from one compartment to another by vesicular traffic. Transport vesicles bud from donor membranes and dock to specific acceptor compartments. The *S. cerevisiae* protein Sec1p participates in the constitutive secretory pathway between the Golgi apparatus and the plasma membrane. Pevsner et al. (1994) identified n-Sec1, a rat brain protein homologous to Sec1p. They found that n-Sec1 is a neural-specific, syntaxin (see OMIM Ref. No. 186590)-binding protein that may participate in the regulation of synaptic vesicle docking and fusion. Animal model experiments lend further support to the function of STXBP1. Verhage et al. (2000) abolished Munc18-1 in mice by homologous recombination. This resulted in a completely paralyzed organism. Null mutant embryos were alive until birth but died immediately after birth, probably because they could not breathe. Despite the general, complete, and permanent

loss of synaptic transmission in knockout mice, their brains were assembled correctly. Neuronal proliferation, migration, and differentiation into specific brain areas were unaffected. By embryonic day 12, brains from null mutant and control littermates were morphologically indistinguishable. At birth, late-forming brain areas such as the neocortex appeared identical in null mutant and control littermates. After initial brain assembly, extensive cell death of mature neurons was observed in null mutants, occurring first in lower brain areas that mature and form synapses relatively early. The degeneration in the mutant brains exhibited all characteristics of apoptosis. Ablation of Munc18-1 renders the brain synaptically silent, identifying Munc18-1 as the currently most upstream essential protein in neurotransmitter release. Verhage et al. (2000) concluded that synaptic connectivity does not depend on neurotransmitter secretion, but its maintenance does. Neurotransmitter secretion probably functions to validate already established synaptic connections.

[28490] It is appreciated that the abovementioned animal model for STXBP1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[28491] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28492] Pevsner, J.; Hsu, S.-C.; Scheller, R. H. : n-Sec1: a neural-specific syntaxin-binding protein. Proc. Nat. Acad. Sci. 91: 1445-1449, 1994. ; and

[28493] Verhage, M.; Mala, A. S.; Plomp, J. J.; Brussaard, A. B.; Heeroma, J. H.; Vermeer, H.; Toonen, R. F.; Hammer, R. E.; van den Berg, T. K.; Missler, M.; Geuze, H. J.; Sudhof, T. C. : Synap.

[28494] Further studies establishing the function and utilities of STXBP1 are found in John Hopkins OMIM database record ID 602926, and in cited publications numbered 176 and 7747-7750 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZp434M0331 (Accession NM\_017600) is another VGAM708 host target gene. DKFZp434M0331 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp434M0331, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434M0331 BINDING SITE, designated



SEQ ID:19075, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28495] Another function of VGAM708 is therefore inhibition of DKFZp434M0331 (Accession NM\_017600). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434M0331. DKFZP547E2110 (Accession XM\_165676) is another VGAM708 host target gene. DKFZP547E2110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP547E2110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP547E2110 BINDING SITE, designated SEQ ID:43733, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28496] Another function of VGAM708 is therefore inhibition of DKFZP547E2110 (Accession XM\_165676). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP547E2110. DRIL2 (Accession NM\_006465) is

another VGAM708 host target gene. DRIL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DRIL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRIL2 BINDING SITE, designated SEQ ID:13193, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28497] Another function of VGAM708 is therefore inhibition of DRIL2 (Accession NM\_006465). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRIL2. FLJ12671 (Accession NM\_030980) is another VGAM708 host target gene. FLJ12671 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ12671, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12671 BINDING SITE, designated SEQ ID:25243, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28498] Another function of VGAM708 is therefore inhibition of FLJ12671 (Accession NM\_030980). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12671. FLJ12891 (Accession NM\_024950) is another VGAM708 host target gene. FLJ12891 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12891, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12891 BINDING SITE, designated SEQ ID:24511, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28499] Another function of VGAM708 is therefore inhibition of FLJ12891 (Accession NM\_024950). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12891. H2A Histone Family, Member J (H2AFJ, Accession NM\_018267) is another VGAM708 host target gene. H2AFJ BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by H2AFJ, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of H2AFJ BINDING SITE, designated SEQ ID:20238, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28500] Another function of VGAM708 is therefore inhibition of H2A Histone Family, Member J (H2AFJ, Accession NM\_018267). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with H2AFJ. KIAA0261 (Accession XM\_042946) is another VGAM708 host target gene. KIAA0261 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0261 BINDING SITE, designated SEQ ID:33836, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28501] Another function of VGAM708 is therefore inhibition of KIAA0261 (Accession XM\_042946). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0261. KIAA1045 (Accession XM\_048592) is another VGAM708 host target gene. KIAA1045 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1045, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1045 BINDING SITE, designated SEQ ID:35202, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28502] Another function of VGAM708 is therefore inhibition of KIAA1045 (Accession XM\_048592). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1045. KIAA1432 (Accession XM\_039698) is another VGAM708 host target gene. KIAA1432 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1432, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1432 BINDING SITE, designated SEQ ID:33154, to the

nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28503] Another function of VGAM708 is therefore inhibition of KIAA1432 (Accession XM\_039698). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1432. MGC11034 (Accession NM\_031453) is another VGAM708 host target gene. MGC11034 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC11034, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC11034 BINDING SITE, designated SEQ ID:25473, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28504] Another function of VGAM708 is therefore inhibition of MGC11034 (Accession NM\_031453). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC11034. RA-GEF-2 (Accession NM\_016340) is another VGAM708 host target gene. RA-GEF-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by RA-GEF-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RA-GEF-2 BINDING SITE, designated SEQ ID:18466, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28505] Another function of VGAM708 is therefore inhibition of RA-GEF-2 (Accession NM\_016340). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RA-GEF-2. LOC145844 (Accession XM\_085255) is another VGAM708 host target gene. LOC145844 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145844, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145844 BINDING SITE, designated SEQ ID:38000, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28506] Another function of VGAM708 is therefore inhibition of LOC145844 (Accession XM\_085255). Accordingly, utilities

of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145844. LOC147180 (Accession XM\_097207) is another VGAM708 host target gene. LOC147180 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147180, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147180 BINDING SITE, designated SEQ ID:40819, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28507] Another function of VGAM708 is therefore inhibition of LOC147180 (Accession XM\_097207). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147180. LOC150933 (Accession XM\_097971) is another VGAM708 host target gene. LOC150933 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150933, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences



of LOC150933 BINDING SITE, designated SEQ ID:41274, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28508] Another function of VGAM708 is therefore inhibition of LOC150933 (Accession XM\_097971). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150933. LOC157450 (Accession XM\_048209) is another VGAM708 host target gene. LOC157450 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157450, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157450 BINDING SITE, designated SEQ ID:35149, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28509] Another function of VGAM708 is therefore inhibition of LOC157450 (Accession XM\_048209). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157450. LOC221486 (Accession XM\_165760) is another VGAM708 host target gene. LOC221486 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221486, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221486 BINDING SITE, designated SEQ ID:43747, to the nucleotide sequence of VGAM708 RNA, herein designated VGAM RNA, also designated SEQ ID:3419.

[28510] Another function of VGAM708 is therefore inhibition of LOC221486 (Accession XM\_165760). Accordingly, utilities of VGAM708 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221486. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 709 (VGAM709) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28511] VGAM709 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM709 was detected is described hereinabove with reference to Figs. 1-8.

[28512] VGAM709 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Helicoverpa Armigera Nuclear Polyhedrosis Virus. VGAM709 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28513] VGAM709 gene encodes a VGAM709 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM709 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM709 precursor RNA is designated SEQ ID:695, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:695 is located at position 70255 relative to the genome of Helicoverpa Armigera Nuclear Polyhedrosis Virus.

[28514] VGAM709 precursor RNA folds onto itself, forming VGAM709 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[28515] An enzyme complex designated DICER COMPLEX, `dices` the VGAM709 folded precursor RNA into VGAM709 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM709 RNA is designated SEQ ID:3420, and is provided hereinbelow with reference to the sequence listing part.

[28516] VGAM709 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM709 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM709 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28517] VGAM709 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM709 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM709 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM709 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM709 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28518] The complementary binding of VGAM709 RNA, herein designated VGAM RNA, to host target binding sites on VGAM709 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM709 host target RNA into VGAM709 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28519] It is appreciated that VGAM709 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM709 host target genes. The mRNA of each one of this plurality of VGAM709 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM709 RNA, herein designated VGAM RNA, and which when bound by VGAM709 RNA causes inhibition of translation of respective one or more VGAM709 host target proteins.

[28520] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM709 gene, herein designated VGAM GENE, on one or more VGAM709 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28521] It is yet further appreciated that a function of VGAM709 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM709 include diagnosis, prevention and treatment of viral infection by Helicoverpa Armigera Nuclear Polyhedrosis Virus. Specific functions, and accordingly utilities, of VGAM709 correlate with, and may be deduced from, the identity of the host target genes which VGAM709 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28522] Nucleotide sequences of the VGAM709 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM709 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM709 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM709 are further described hereinbelow with reference to Table 1.

[28523] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM709 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM709 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28524] As mentioned hereinabove with reference to Fig. 1, a function of VGAM709 gene, herein designated VGAM is inhibition of expression of VGAM709 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM709 correlate with, and may be deduced from, the identity of the target genes which VGAM709 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28525] RALBP1 Associated Eps Domain Containing 2 (REPS2, Accession NM\_004726) is a VGAM709 host target gene. REPS2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by REPS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2



illustrates the complementarity of the nucleotide sequences of REPS2 BINDING SITE, designated SEQ ID:11097, to the nucleotide sequence of VGAM709 RNA, herein designated VGAM RNA, also designated SEQ ID:3420.

[28526] A function of VGAM709 is therefore inhibition of RALBP1 Associated Eps Domain Containing 2 (REPS2, Accession NM\_004726), a gene which interacts with the active form of RAS with adaptor protein GRB2 and binds calcium. Accordingly, utilities of VGAM709 include diagnosis, prevention and treatment of diseases and clinical conditions associated with REPS2. The function of REPS2 has been established by previous studies. Small G proteins have GDP-bound inactive and GTP-bound active forms; RAL proteins (e.g., RALA; 179550) shift from the inactive to the active state through the actions of RALGDS (OMIM Ref. No. 601619). RALGDS interacts with the active form of RAS (see OMIM Ref. No. HRAS; 190020). Using RALA-binding protein-1 (RALBP1; 605801) as bait in a yeast 2-hybrid screen of a brain cDNA library, Ikeda et al. (1998) isolated cDNAs encoding REPS2, which they termed POB1. Sequence analysis predicted that the 521-amino acid protein has 2 potential initiator methionines in its N termi-

nus, a central EPS15 (OMIM Ref. No. 600051)–like domain, and 2 proline–rich regions and a putative coiled–coil structure in its C terminus. Northern blot analysis revealed strong expression in rat cerebrum, cerebellum, lung, and testis, with weak expression in kidney and no expression in heart, thymus, liver, spleen, or adrenal gland. Immuno–precipitation and immunoblot analyses confirmed that the C–terminal 146 amino acids of REPS2 and the C–terminal 147 residues of RALBP1 interact in intact cells. RAL interacts with a distinct region of RALBP1, just N terminal of the REPS2–binding domain, and both proteins can interact simultaneously with RALBP1. Immunoblot analysis established that REPS2 is tyrosine phosphorylated in response to epidermal growth factor (EGF; 131530) and interacts with the EGF receptor (EGFR; 131550), possibly through the adaptor protein GRB2 (OMIM Ref. No. 108355), with which REPS2 interacts specifically. Using nuclear magnetic resonance spectroscopy, Koshihara et al. (1999) showed that the EPS15 homology domain of REPS2 consists of 2 EF–hand structures, the second of which binds calcium.

[28527] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [28528] Ikeda, M.; Ishida, O.; Hinoi, T.; Kishida, S.; Kikuchi, A. : Identification and characterization of a novel protein interacting with Ral-binding protein 1, a putative effector protein of Ral. *J. Biol. Chem.* 273: 814–821, 1998. ; and
- [28529] Koshiba, S.; Kigawa, T.; Iwahara, J.; Kikuchi, A.; Yokoyama, S. : Solution structure of the Eps15 homology domain of a human POB1 (partner of RalBP1). *FEBS Lett.* 442: 138–142, 1999.
- [28530] Further studies establishing the function and utilities of REPS2 are found in John Hopkins OMIM database record ID 300317, and in cited publications numbered 9445–9446 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transient Receptor Potential Cation Channel, Subfamily M, Member 8 (TRPM8, Accession NM\_024080) is another VGAM709 host target gene. TRPM8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPM8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPM8 BINDING SITE, designated SEQ ID:23514, to the nucleotide sequence of VGAM709 RNA, herein designated VGAM RNA, also designated SEQ

ID:3420.

[28531] Another function of VGAM709 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily M, Member 8 (TRPM8, Accession NM\_024080), a gene which is thought to form a receptor-activated calcium permeant cation channel. Accordingly, utilities of VGAM709 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPM8. The function of TRPM8 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM201.LOC199923 (Accession XM\_114057) is another VGAM709 host target gene. LOC199923 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199923 BINDING SITE, designated SEQ ID:42667, to the nucleotide sequence of VGAM709 RNA, herein designated VGAM RNA, also designated SEQ ID:3420.

[28532] Another function of VGAM709 is therefore inhibition of LOC199923 (Accession XM\_114057). Accordingly, utilities

of VGAM709 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199923. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 710 (VGAM710) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28533] VGAM710 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM710 was detected is described hereinabove with reference to Figs. 1–8.

[28534] VGAM710 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pestivirus Type 2. VGAM710 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28535] VGAM710 gene encodes a VGAM710 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM710 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM710 precursor RNA is designated SEQ ID:696, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:696 is located at position 4562 relative to the genome of Pestivirus Type 2.

[28536] VGAM710 precursor RNA folds onto itself, forming VGAM710 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28537] An enzyme complex designated DICER COMPLEX, `dices` the VGAM710 folded precursor RNA into VGAM710 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM710 RNA is designated SEQ ID:3421, and

is provided hereinbelow with reference to the sequence listing part.

[28538] VGAM710 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM710 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM710 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28539] VGAM710 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM710 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM710 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM710 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM710 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28540] The complementary binding of VGAM710 RNA, herein designated VGAM RNA, to host target binding sites on VGAM710 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM710 host target RNA into VGAM710 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28541] It is appreciated that VGAM710 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM710 host target genes. The mRNA of each one of this plurality of VGAM710 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-



plementary to VGAM710 RNA, herein designated VGAM RNA, and which when bound by VGAM710 RNA causes inhibition of translation of respective one or more VGAM710 host target proteins.

[28542] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM710 gene, herein designated VGAM GENE, on one or more VGAM710 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28543] It is yet further appreciated that a function of VGAM710 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of viral infection by Pestivirus Type 2. Specific functions, and accordingly utilities, of VGAM710 correlate with, and may be deduced from, the identity of the host target genes which VGAM710 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28544] Nucleotide sequences of the VGAM710 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM710 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM710 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM710 are further described hereinbelow with reference to Table 1.

[28545] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM710 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM710 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28546] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM710 gene, herein designated VGAM is inhibition of expression of VGAM710 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM710 correlate with, and may be deduced from, the identity of the target genes which VGAM710 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28547] Periaxin (PRX, Accession NM\_020956) is a VGAM710 host target gene. PRX BINDING SITE1 and PRX BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PRX, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRX BINDING SITE1 and PRX BINDING SITE2, designated SEQ ID:21936 and SEQ ID:21942 respectively, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28548] A function of VGAM710 is therefore inhibition of Periaxin (PRX, Accession NM\_020956), a gene which seems to be required for maintenance of peripheral nerve myelin sheath. may have a role in axon–glial interactions, possibly by interacting with the cytoplasmic domains of integral membrane proteins such as myelin–associated glycoprotein in the periaxonal regions of the schwann cell plasma membrane. may have a role in the early phases of myelin deposition. Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRX. The function of PRX and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM476.FLJ14082 (Accession NM\_025024) is another VGAM710 host target gene. FLJ14082 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14082, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14082 BINDING SITE, designated SEQ ID:24612, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ

ID:3421.

[28549] Another function of VGAM710 is therefore inhibition of FLJ14082 (Accession NM\_025024). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14082. KIAA0444 (Accession XM\_030999) is another VGAM710 host target gene. KIAA0444 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0444, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0444 BINDING SITE, designated SEQ ID:31244, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28550] Another function of VGAM710 is therefore inhibition of KIAA0444 (Accession XM\_030999). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0444. KIAA0574 (Accession XM\_045076) is another VGAM710 host target gene. KIAA0574 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0574, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0574 BINDING SITE, designated SEQ ID:34348, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28551] Another function of VGAM710 is therefore inhibition of KIAA0574 (Accession XM\_045076). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0574. KIAA1209 (Accession XM\_027307) is another VGAM710 host target gene. KIAA1209 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1209, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1209 BINDING SITE, designated SEQ ID:30471, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28552] Another function of VGAM710 is therefore inhibition of KIAA1209 (Accession XM\_027307). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1209. P450RAI-2 (Accession NM\_019885) is another VGAM710 host target gene. P450RAI-2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by P450RAI-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P450RAI-2 BINDING SITE, designated SEQ ID:21271, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28553] Another function of VGAM710 is therefore inhibition of P450RAI-2 (Accession NM\_019885). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P450RAI-2. RAB, Member of RAS Oncogene Family-like 4 (RABL4, Accession NM\_006860) is another VGAM710 host target gene. RABL4 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RABL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RABL4 BINDING SITE, designated SEQ

ID:13729, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28554] Another function of VGAM710 is therefore inhibition of RAB, Member of RAS Oncogene Family-like 4 (RABL4, Accession NM\_006860). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RABL4. SEC61A1 (Accession NM\_013336) is another VGAM710 host target gene. SEC61A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEC61A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC61A1 BINDING SITE, designated SEQ ID:14986, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28555] Another function of VGAM710 is therefore inhibition of SEC61A1 (Accession NM\_013336). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEC61A1. T-cell Leukemia/lymphoma 6 (TCL6, Accession



NM\_020553) is another VGAM710 host target gene. TCL6 BINDING SITE1 and TCL6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TCL6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCL6 BINDING SITE1 and TCL6 BINDING SITE2, designated SEQ ID:21776 and SEQ ID:21778 respectively, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28556] Another function of VGAM710 is therefore inhibition of T-cell Leukemia/lymphoma 6 (TCL6, Accession NM\_020553). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCL6. LOC257596 (Accession XM\_175296) is another VGAM710 host target gene. LOC257596 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257596, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257596 BINDING SITE, desig-

nated SEQ ID:46753, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28557] Another function of VGAM710 is therefore inhibition of LOC257596 (Accession XM\_175296). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257596. LOC63923 (Accession XM\_040527) is another VGAM710 host target gene. LOC63923 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC63923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC63923 BINDING SITE, designated SEQ ID:33323, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28558] Another function of VGAM710 is therefore inhibition of LOC63923 (Accession XM\_040527). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC63923. LOC92080 (Accession XM\_042704) is another VGAM710 host target gene. LOC92080 BINDING SITE is

HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92080, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92080 BINDING SITE, designated SEQ ID:33760, to the nucleotide sequence of VGAM710 RNA, herein designated VGAM RNA, also designated SEQ ID:3421.

[28559] Another function of VGAM710 is therefore inhibition of LOC92080 (Accession XM\_042704). Accordingly, utilities of VGAM710 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92080. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 711 (VGAM711) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28560] VGAM711 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM711 was detected is described hereinabove with reference to Figs. 1-8.

[28561] VGAM711 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pestivirus Type 2.

VGAM711 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28562] VGAM711 gene encodes a VGAM711 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM711 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM711 precursor RNA is designated SEQ ID:697, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:697 is located at position 2306 relative to the genome of Pestivirus Type 2.

[28563] VGAM711 precursor RNA folds onto itself, forming VGAM711 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[28564] An enzyme complex designated DICER COMPLEX, `dices` the VGAM711 folded precursor RNA into VGAM711 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 86%) nucleotide sequence of VGAM711 RNA is designated SEQ ID:3422, and is provided hereinbelow with reference to the sequence listing part.

[28565] VGAM711 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM711 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM711 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28566] VGAM711 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM711 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM711 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM711 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM711 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28567] The complementary binding of VGAM711 RNA, herein designated VGAM RNA, to host target binding sites on VGAM711 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM711 host target RNA into VGAM711 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28568] It is appreciated that VGAM711 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM711 host target genes. The mRNA of each one of this plurality of VGAM711 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM711 RNA, herein designated VGAM RNA, and which when bound by VGAM711 RNA causes inhibition of translation of respective one or more VGAM711 host target proteins.

[28569] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM711 gene, herein designated VGAM GENE, on one or more VGAM711 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28570] It is yet further appreciated that a function of VGAM711 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of viral infection by Pestivirus Type 2. Specific functions, and accordingly utilities, of VGAM711 correlate with, and may be deduced from, the identity of the host target genes which VGAM711 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28571] Nucleotide sequences of the VGAM711 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM711 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM711 folded precursor RNA, herein designated



VGAM FOLDED PRECURSOR RNA, of VGAM711 are further described hereinbelow with reference to Table 1.

[28572] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM711 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM711 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28573] As mentioned hereinabove with reference to Fig. 1, a function of VGAM711 gene, herein designated VGAM is inhibition of expression of VGAM711 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM711 correlate with, and may be deduced from, the identity of the target genes which VGAM711 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28574] ATPase, Ca++ Transporting, Plasma Membrane 2 (ATP2B2, Accession NM\_001683) is a VGAM711 host target gene. ATP2B2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ATP2B2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of ATP2B2 BINDING SITE, designated SEQ ID:7404, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28575] A function of VGAM711 is therefore inhibition of ATPase, Ca++ Transporting, Plasma Membrane 2 (ATP2B2, Accession NM\_001683), a gene which catalyzes the hydrolysis of ATP coupled with the transport of the calcium out of the cell . Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP2B2. The function of ATP2B2 has been established by previous studies. Street et al. (1998) demonstrated that the deafwaddler (dfw) mouse mutant, which is deaf and displays vestibular/motor imbalance, has a mutation in the Atp2b2 gene. A A-to-G nucleotide transition in dfw DNA caused a glycine-to-serine substitution at a highly conserved amino acid position, whereas a second mutant allele carried a 2-bp deletion that caused a frameshift predicted to result in a truncated protein. In the cochlea, the Atp2b2 protein is localized to stereocilia and the basolateral wall of hair cells in wildtype mice, but is not detected in deafwaddler

mice. This indicates that mutation of Atp2b2 may cause deafness and imbalance by affecting sensory transduction in stereocilia as well as neurotransmitter release from the basolateral membrane. These mutations affecting Atp2b2 were the first to be found in a mammalian plasma membrane calcium pump and defined a new class of deafness genes that directly affect hair-cell physiology. PMCA2 exhibits a highly restricted tissue distribution, suggesting that it serves more specialized physiologic functions than some of the other PMCA isoforms. A unique role in hearing is suggested by the high levels of PMCA2 expression in cochlear outer hair cells and spiral ganglion cells. Animal model experiments lend further support to the function of ATP2B2. To analyze the physiologic role of PMCA2, Kozel et al. (1998) produced PMCA2-deficient mice by gene targeting. Homozygous PMCA2-null mice grew more slowly than heterozygous and wildtype mice and exhibited an unsteady gait and difficulties in maintaining balance. Histologic analysis of the cerebellum and inner ear of mutant and wildtype mice showed that null mutants have slightly increased numbers of Purkinje neurons (in which PMCA2 is highly expressed), a decreased thickness of the molecular layer, an absence of otoconia in the vestibular

system, and a range of abnormalities of the organ of Corti. Analysis of auditory-evoked brain stem responses showed that homozygous mutants were deaf and that heterozygous mice had a significant hearing loss. These data demonstrated that PMCA2 is required for both balance and hearing and suggested that it may be a major source of the calcium used in the formation and maintenance of otoconia.

[28576] It is appreciated that the abovementioned animal model for ATP2B2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[28577] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28578] Street, V. A.; McKee-Johnson, J. W.; Fonseca, R. C.; Tempel, B. L.; Noben-Trauth, K. : Mutations in a plasma membrane  $\text{Ca}(2+)$ -ATPase gene cause deafness in deafwaddler mice. *Nature Genet.* 19: 390-394, 1998. ; and

[28579] Kozel, P. J.; Friedman, R. A.; Erway, L. C.; Yamoah, E. N.; Liu, L. H.; Riddle, T.; Duffy, J. J.; Doetschman, T.; Miller, M. L.; Cardell, E. L.; Shull, G. E. : Balance and hearing defic.

[28580] Further studies establishing the function and utilities of

ATP2B2 are found in John Hopkins OMIM database record ID 108733, and in cited publications numbered 3692–3696 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Down-regulator of Transcription 1, TBP-binding (negative cofactor 2) (DR1, Accession XM\_002015) is another VGAM711 host target gene. DR1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DR1 BINDING SITE, designated SEQ ID:29856, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28581] Another function of VGAM711 is therefore inhibition of Down-regulator of Transcription 1, TBP-binding (negative cofactor 2) (DR1, Accession XM\_002015), a gene which influences functional repression of both activated and basal transcription of class ii genes. Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DR1. The function of DR1 has been established by previous

studies. Several phosphoproteins are known to interact with TBP, the TATA box-binding protein (OMIM Ref. No. 600075). Among them, DR1 is a TBP-associated phosphoprotein that represses both basal and activated levels of transcription. Inostroza et al. (1992) biochemically characterized DR1 purified from HeLa cells and cloned the human gene from a HeLa cell cDNA library. The gene encodes a 176-amino acid polypeptide of 19 kD. They showed that DR1 is phosphorylated in vivo and that phosphorylation of DR1 affected its interaction with TBP. The DR1 protein contains 3 domains: a histone fold motif at the N terminus, a TBP-binding domain, and a glutamine- and alanine-rich region. Mermelstein et al. (1996) showed that the histone fold motif of DR1 is required for DR1-DRAP1 interaction. Both the TBP-binding domain and the glutamine- and alanine-rich region are required for DR1-mediated repression of transcription. Yeung et al. (1997) demonstrated that the TBP-binding domain has 2 functions: it tethers the DR1 repressor complex to the promoter by interacting with TBP, and it is required for the corepression activity of DRAP1, although it is not required for DR1-DRAP1 interaction. Yeung et al. (1997) determined that the glutamine- and alanine-rich region is the

repressor domain of DR1 and that this domain interacts with TBP. Goppelt et al. (1996) proposed that binding of DR1 repressor complexes to TBP-promoter complexes establishes a mechanism in which an altered DNA conformation, together with the formation of higher order complexes, inhibits the assembly of the preinitiation complex and controls the rate of RNA polymerase II transcription.

[28582] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28583] Inostroza, J. A.; Mermeistein, F. H.; Ha, I.; Lane, W. S.; Reinberg, D. : Dr1, a TATA-binding protein-associated phosphoprotein and inhibitor of class II gene transcription. Cell 70: 477-489, 1992. ; and

[28584] Mermelstein, F.; Yeung, K.; Cao, J.; Inostroza, J. A.; Erdjument-Bromage, H.; Egelson, K.; Landsman, D.; Levitt, P.; Tempst, P.; Reinberg, D. : Requirement of a corepressor for Dr1-med.

[28585] Further studies establishing the function and utilities of DR1 are found in John Hopkins OMIM database record ID 601482, and in cited publications numbered 6516-651 and 9241-6523 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer-

ence. E2F Transcription Factor 1 (E2F1, Accession XM\_097772) is another VGAM711 host target gene. E2F1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by E2F1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of E2F1 BINDING SITE, designated SEQ ID:41119, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28586] Another function of VGAM711 is therefore inhibition of E2F Transcription Factor 1 (E2F1, Accession XM\_097772), a gene which involved in cell cycle regulation, mediates G1 arrest when bound to Rb. Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with E2F1. The function of E2F1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM430. Fatty Acid Amide Hydrolase (FAAH, Accession NM\_024306) is another VGAM711 host target gene. FAAH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FAAH, corre-



sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FAAH BINDING SITE, designated SEQ ID:23596, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28587] Another function of VGAM711 is therefore inhibition of Fatty Acid Amide Hydrolase (FAAH, Accession NM\_024306), a gene which function as an electron carrier for several membrane bound oxygenases (by similarity). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FAAH. The function of FAAH has been established by previous studies. To evaluate FAAH genes as candidates for neurogenetic diseases in humans and mice, Wan et al. (1998) mapped the loci in both species and determined their intron-exon structures using PCR analysis of somatic cell hybrids and radiation hybrid mapping panels. Analysis of a somatic cell hybrid mapping panel and a mouse interspecific backcross panel localized the Faah gene to the conserved syntenic region on mouse chromosome 4, close to the neurologic mutation 'clasper.' No sequence abnormality or rearrangement of the Faah gene

was found to explain the clasper phenotype. Furthermore, FAAH protein levels were normal in clasper mouse tissues. Problem drug use and dependence are neurobehavioral disorders of complex origin. Although environmental factors contribute to drug abuse and addiction, genetic factors play a significant role estimated at 40 to 60% of the total risk. In the course of a search for the human genes that confer vulnerability to problem drug use, Sipe et al. (2002) identified a single-nucleotide polymorphism (SNP) in the FAAH gene, that in homozygous form is strongly associated with both street drug use and problem drug/alcohol use. This SNP (OMIM Ref. No. 385C-A) results in a missense mutation that converts a conserved proline residue to threonine (pro129 OMIM Ref. No. 602935.0001), producing an FAAH variant that displays normal catalytic properties but at enhanced sensitivity to proteolytic degradation. Collectively, these results suggested that genetic mutations in FAAH may constitute important risk factors for problem drug use and support a potential link between functional abnormalities in the endogenous cannabinoid system and drug abuse and dependence.

[28588] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [28589] Sipe, J. C.; Chiang, K.; Gerber, A. L.; Beutler, E.; Cravatt, B. F. : A missense mutation in human fatty acid amide hydrolase associated with problem drug use. Proc. Nat. Acad. Sci. 99: 8394–8399, 2002. ; and
- [28590] Wan, M.; Cravatt, B. F.; Ring, H. Z.; Zhang, X.; Francke, U. : Conserved chromosomal location and genomic structure of human and mouse fatty-acid amide hydrolase genes and evaluation of.
- [28591] Further studies establishing the function and utilities of FAAH are found in John Hopkins OMIM database record ID 602935, and in cited publications numbered 7974–7977 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Sorbin and SH3 Domain Containing 1 (SORBS1, Accession NM\_015385) is another VGAM711 host target gene. SORBS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SORBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SORBS1 BINDING SITE, designated SEQ ID:17686, to the nucleotide

sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28592] Another function of VGAM711 is therefore inhibition of Sorbin and SH3 Domain Containing 1 (SORBS1, Accession NM\_015385), a gene which necessary for cell polarization during vegetative growth. Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORBS1. The function of SORBS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM475. TYRO3 Protein Tyrosine Kinase (TYRO3, Accession NM\_006293) is another VGAM711 host target gene. TYRO3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TYRO3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TYRO3 BINDING SITE, designated SEQ ID:12985, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28593] Another function of VGAM711 is therefore inhibition of

TYRO3 Protein Tyrosine Kinase (TYRO3, Accession NM\_006293), a gene which may be involved in cell adhesion processes, particularly in the central nervous system. Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TYRO3. The function of TYRO3 has been established by previous studies. Polvi et al. (1993) cloned partial cDNAs of the human TYRO3 gene encoding a putative receptor tyrosine kinase and its processed pseudogene (OMIM Ref. No. TYRO3P) from human teratocarcinoma cell, bone marrow, and melanocyte cDNA libraries. The tyrosine kinase homologous domains of the 2 genes were sequenced and compared with each other and with the mouse Tyro3 gene. Abundant levels of the 4.2-kb TYRO3 mRNA were detected in human brain and lower levels in other human tissues. Animal model experiments lend further support to the function of TYRO3. Regulation of lymphocyte numbers is mediated by cytokines signaling through receptors coupled to cytoplasmic protein-tyrosine kinases. Lu and Lemke (2001) generated mice deficient in Mertk (OMIM Ref. No. 604705), Axl (OMIM Ref. No. 109135), and Tyro3. Like their ligands, GAS6 (OMIM Ref. No. 600441) and PROS1 (OMIM Ref. No. 176880),

these receptors are widely expressed in monocytes and macrophages but not in B or T lymphocytes. Although the peripheral lymphoid organs of mutant mice were indistinguishable from those of wildtype mice at birth, by 4 weeks of age spleens and lymph nodes grew at elevated rates. This was primarily due to the hyperproliferation of constitutively activated B and T cells, particularly CD4-positive T cells, with ectopic colonies in every adult organ examined. All triple mutants developed autoimmunity with symptoms histologically similar to human rheumatoid arthritis (OMIM Ref. No. 180300), pemphigus vulgaris (OMIM Ref. No. 169610), and systemic lupus erythematosus (OMIM Ref. No. 152700), and were characterized by antibodies against normal cellular antigens, including phospholipids and double-stranded DNA. Females were particularly prone to thromboses and recurrent fetal loss. Flow cytometric analysis demonstrated that wildtype B and T cells underwent multiple rounds of cell division after injection into mutant mice and that their antigen-presenting cells expressed elevated levels of activation markers. Lu and Lemke (2001) proposed that the cells that initiate lymphoproliferation and autoimmunity in the Tyro3 family mutants were the macrophages and dendritic cells that

normally express the 3 receptor genes.

[28594] It is appreciated that the abovementioned animal model for TYRO3 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[28595] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28596] Polvi, A.; Armstrong, E.; Lai, C.; Lemke, G.; Huebner, K.; Spritz, R. A.; Guida, L. C.; Nicholls, R. D.; Alitalo, K. : The human TYRO3 gene and pseudogene are located in chromosome 15q14–q25. *Gene* 134: 289–293, 1993. ; and

[28597] Lu, Q.; Lemke, G. : Homeostatic regulation of the immune system by receptor tyrosine kinases of the Tyro 3 family. *Science* 293: 306–311, 2001.

[28598] Further studies establishing the function and utilities of TYRO3 are found in John Hopkins OMIM database record ID 600341, and in cited publications numbered 507 and 12302 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ubiquitin–conjugating Enzyme E2L 3 (UBE2L3, Accession NM\_003347) is another VGAM711 host target gene. UBE2L3 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by UBE2L3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2L3 BINDING SITE, designated SEQ ID:9357, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28599] Another function of VGAM711 is therefore inhibition of Ubiquitin-conjugating Enzyme E2L 3 (UBE2L3, Accession NM\_003347), a gene which catalyzes the covalent attachment of ubiquitin to other proteins. Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2L3. The function of UBE2L3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM215. Chromosome 1 Open Reading Frame 34 (C1orf34, Accession XM\_027172) is another VGAM711 host target gene. C1orf34 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1orf34, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-



ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1orf34 BINDING SITE, designated SEQ ID:30438, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28600] Another function of VGAM711 is therefore inhibition of Chromosome 1 Open Reading Frame 34 (C1orf34, Accession XM\_027172). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf34. FLJ13305 (Accession XM\_117270) is another VGAM711 host target gene. FLJ13305 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ13305, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13305 BINDING SITE, designated SEQ ID:43344, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28601] Another function of VGAM711 is therefore inhibition of FLJ13305 (Accession XM\_117270). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ13305. KIAA1634 (Accession XM\_032749) is another VGAM711 host target gene. KIAA1634 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1634, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1634 BINDING SITE, designated SEQ ID:31753, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28602] Another function of VGAM711 is therefore inhibition of KIAA1634 (Accession XM\_032749). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1634. MGC11287 (Accession NM\_031464) is another VGAM711 host target gene. MGC11287 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC11287, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC11287 BINDING SITE, designated SEQ ID:25502, to

the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28603] Another function of VGAM711 is therefore inhibition of MGC11287 (Accession NM\_031464). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC11287. P114-RHO-GEF (Accession NM\_015318) is another VGAM711 host target gene. P114-RHO-GEF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P114-RHO-GEF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P114-RHO-GEF BINDING SITE, designated SEQ ID:17638, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28604] Another function of VGAM711 is therefore inhibition of P114-RHO-GEF (Accession NM\_015318). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P114-RHO-GEF. Protein Phosphatase 1, Regulatory (inhibitor) Subunit 16B (PPP1R16B, Accession XM\_028840)

is another VGAM711 host target gene. PPP1R16B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1R16B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R16B BINDING SITE, designated SEQ ID:30770, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28605] Another function of VGAM711 is therefore inhibition of Protein Phosphatase 1, Regulatory (inhibitor) Subunit 16B (PPP1R16B, Accession XM\_028840). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R16B. Retinoic Acid Induced 16 (RAI16, Accession NM\_022749) is another VGAM711 host target gene. RAI16 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAI16, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAI16 BINDING SITE, designated SEQ ID:22969, to the nucleotide sequence of VGAM711 RNA, herein designated

VGAM RNA, also designated SEQ ID:3422.

[28606] Another function of VGAM711 is therefore inhibition of Retinoic Acid Induced 16 (RAI16, Accession NM\_022749). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAI16. T-cell Lymphoma Invasion and Metastasis 2 (TIAM2, Accession NM\_012454) is another VGAM711 host target gene. TIAM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIAM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIAM2 BINDING SITE, designated SEQ ID:14824, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28607] Another function of VGAM711 is therefore inhibition of T-cell Lymphoma Invasion and Metastasis 2 (TIAM2, Accession NM\_012454). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIAM2. Translocase of Inner Mitochondrial Membrane 9 Homolog (yeast) (TIMM9, Accession NM\_012460) is another VGAM711 host target

gene. TIMM9 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TIMM9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMM9 BINDING SITE, designated SEQ ID:14832, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28608] Another function of VGAM711 is therefore inhibition of Translocase of Inner Mitochondrial Membrane 9 Homolog (yeast) (TIMM9, Accession NM\_012460). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIMM9. LOC112868 (Accession XM\_053402) is another VGAM711 host target gene. LOC112868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC112868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112868 BINDING SITE, designated SEQ ID:36077, to the nucleotide sequence of VGAM711 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3422.

[28609] Another function of VGAM711 is therefore inhibition of LOC112868 (Accession XM\_053402). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112868. LOC116228 (Accession XM\_057659) is another VGAM711 host target gene. LOC116228 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC116228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC116228 BINDING SITE, designated SEQ ID:36534, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28610] Another function of VGAM711 is therefore inhibition of LOC116228 (Accession XM\_057659). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116228. LOC201910 (Accession XM\_114403) is another VGAM711 host target gene. LOC201910 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201910, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201910 BINDING SITE, designated SEQ ID:42929, to the nucleotide sequence of VGAM711 RNA, herein designated VGAM RNA, also designated SEQ ID:3422.

[28611] Another function of VGAM711 is therefore inhibition of LOC201910 (Accession XM\_114403). Accordingly, utilities of VGAM711 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201910. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 712 (VGAM712) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28612] VGAM712 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM712 was detected is described hereinabove with reference to Figs. 1–8.

[28613] VGAM712 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pestivirus Type 2.



VGAM712 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28614] VGAM712 gene encodes a VGAM712 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM712 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM712 precursor RNA is designated SEQ ID:698, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:698 is located at position 2668 relative to the genome of Pestivirus Type 2.

[28615] VGAM712 precursor RNA folds onto itself, forming VGAM712 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28616] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM712 folded precursor RNA into VGAM712 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM712 RNA is designated SEQ ID:3423, and is provided hereinbelow with reference to the sequence listing part.

[28617] VGAM712 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM712 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM712 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28618] VGAM712 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM712 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM712 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM712 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM712 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28619] The complementary binding of VGAM712 RNA, herein designated VGAM RNA, to host target binding sites on VGAM712 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM712 host target RNA into VGAM712 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28620] It is appreciated that VGAM712 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM712 host target genes. The mRNA of each one of this plurality of VGAM712 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM712 RNA, herein designated VGAM RNA, and which when bound by VGAM712 RNA causes inhibition of translation of respective one or more VGAM712 host target proteins.

[28621] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM712 gene, herein designated VGAM GENE, on one or more VGAM712 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28622] It is yet further appreciated that a function of VGAM712 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM712 include diagnosis, prevention and treatment of viral infection by Pestivirus Type 2. Specific functions, and accordingly utilities, of VGAM712 correlate with, and may be deduced from, the identity of the host target genes which VGAM712 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28623] Nucleotide sequences of the VGAM712 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM712 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM712 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM712 are further described hereinbelow with reference to Table 1.

[28624] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM712 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM712 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28625] As mentioned hereinabove with reference to Fig. 1, a function of VGAM712 gene, herein designated VGAM is inhibition of expression of VGAM712 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM712 correlate with, and may be deduced from, the identity of the target genes which VGAM712 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28626] DKFZp566D234 (Accession XM\_030162) is a VGAM712 host target gene. DKFZp566D234 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp566D234, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp566D234 BINDING SITE, designated SEQ ID:30991, to

the nucleotide sequence of VGAM712 RNA, herein designated VGAM RNA, also designated SEQ ID:3423.

[28627] A function of VGAM712 is therefore inhibition of DKFZp566D234 (Accession XM\_030162). Accordingly, utilities of VGAM712 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp566D234. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 713 (VGAM713) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28628] VGAM713 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM713 was detected is described hereinabove with reference to Figs. 1–8.

[28629] VGAM713 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Herpesvirus 4. VGAM713 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28630] VGAM713 gene encodes a VGAM713 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM713 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM713 precursor RNA is designated SEQ ID:699, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:699 is located at position 103800 relative to the genome of Bovine Herpesvirus 4.

[28631] VGAM713 precursor RNA folds onto itself, forming VGAM713 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28632] An enzyme complex designated DICER COMPLEX, `dices` the VGAM713 folded precursor RNA into VGAM713 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short



~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM713 RNA is designated SEQ ID:3424, and is provided hereinbelow with reference to the sequence listing part.

[28633] VGAM713 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM713 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM713 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[28634] VGAM713 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM713 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM713 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM713 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM713 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28635] The complementary binding of VGAM713 RNA, herein designated VGAM RNA, to host target binding sites on VGAM713 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM713 host target RNA into VGAM713 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28636] It is appreciated that VGAM713 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM713 host target genes. The mRNA of each one of this plurality of VGAM713 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM713 RNA, herein designated VGAM RNA, and which when bound by VGAM713 RNA causes inhibition of translation of respective one or more VGAM713 host target proteins.

[28637] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM713 gene, herein designated VGAM GENE, on one or more VGAM713 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[28638] It is yet further appreciated that a function of VGAM713 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of viral infection by Bovine Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM713 correlate with, and may be deduced from, the identity of the host target genes which VGAM713 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28639] Nucleotide sequences of the VGAM713 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM713 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM713 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM713 are further described hereinbelow with reference to Table 1.

[28640] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM713 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM713 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28641] As mentioned hereinabove with reference to Fig. 1, a function of VGAM713 gene, herein designated VGAM is inhibition of expression of VGAM713 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM713 correlate with, and may be deduced from, the identity of the target genes which VGAM713 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28642] Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 1; Cyclin D-related (CBFA2T1, Accession NM\_004349) is a VGAM713 host target gene. CBFA2T1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CBFA2T1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CBFA2T1 BINDING SITE, designated SEQ ID:10544, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28643] A function of VGAM713 is therefore inhibition of Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 1; Cyclin D-related (CBFA2T1, Accession NM\_004349), a gene which produces a chimeric gene made up of the 5-prime region of the AML1 gene fused to the 3-prime region of the ETO gene through translocation. Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBFA2T1. The function of CBFA2T1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM113.

Diacylglycerol O-acyltransferase Homolog 2 (mouse) (DGAT2, Accession NM\_032564) is another VGAM713 host target gene. DGAT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DGAT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGAT2 BINDING SITE, designated SEQ ID:26293, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28644] Another function of VGAM713 is therefore inhibition of Diacylglycerol O-acyltransferase Homolog 2 (mouse) (DGAT2, Accession NM\_032564). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DGAT2. Interleukin 24 (IL24, Accession NM\_006850) is another VGAM713 host target gene. IL24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL24 BINDING SITE, designated SEQ ID:13721, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28645] Another function of VGAM713 is therefore inhibition of Interleukin 24 (IL24, Accession NM\_006850), a gene which may contribute to terminal cell differentiation. Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL24. The function of IL24 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove

with reference to VGAM258. Microtubule-associated Protein, RP/EB Family, Member 1 (MAPRE1, Accession NM\_012325) is another VGAM713 host target gene. MAPRE1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAPRE1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPRE1 BINDING SITE, designated SEQ ID:14707, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28646] Another function of VGAM713 is therefore inhibition of Microtubule-associated Protein, RP/EB Family, Member 1 (MAPRE1, Accession NM\_012325). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPRE1. Neogenin Homolog 1 (chicken) (NEO1, Accession NM\_002499) is another VGAM713 host target gene. NEO1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-



trates the complementarity of the nucleotide sequences of NEO1 BINDING SITE, designated SEQ ID:8316, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28647] Another function of VGAM713 is therefore inhibition of Neogenin Homolog 1 (chicken) (NEO1, Accession NM\_002499), a gene which regulates the transition of undifferentiated proliferating cells to their differentiated state. Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEO1. The function of NEO1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM329. Phosphotriesterase Related (PTER, Accession NM\_030664) is another VGAM713 host target gene. PTER BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTER, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTER BINDING SITE, designated SEQ ID:25000, to the nucleotide sequence of VGAM713 RNA, herein designated

VGAM RNA, also designated SEQ ID:3424.

[28648] Another function of VGAM713 is therefore inhibition of Phosphotriesterase Related (PTER, Accession NM\_030664), a gene which is a phosphotriesterase homology protein. Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTER. The function of PTER has been established by previous studies. Microbial phosphotriesterases are a group of zinc metalloenzymes that catalyze the hydrolysis of a range of phosphotriester compounds. Davies et al. (1997) isolated rat cDNAs encoding a phosphotriesterase homolog, which they named rpr1. Using a rat rpr1 cDNA as a hybridization probe, Alimova-Kost et al. (1998) isolated human genomic sequences of PTER, a homolog of phosphotriesterases. By FISH, Alimova-Kost et al. (1998) mapped the human PTER gene to 10p12

[28649] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28650] Alimova-Kost, M. V.; Imreh, S.; Buchman, V. L.; Ninkina, N. N. : Assignment of phosphotriesterase-related gene (PTER) to human chromosome band 10p12 by in situ hy-

bridization. Cytogenet. Cell Genet. 83: 16–17, 1998. ; and

[28651] Davies, J. A.; Buchman, V. L.; Krylova, O.; Ninkina, N. N. :  
Molecular cloning and expression pattern of rpr-1, a  
resiniferatoxin-binding, phosphotriesterase-related pro-  
tein, expressed.

[28652] Further studies establishing the function and utilities of  
PTER are found in John Hopkins OMIM database record ID  
604446, and in cited publications numbered 1096–1097  
listed in the bibliography section hereinbelow, which are  
also hereby incorporated by reference. Recombination Ac-  
tivating Gene 1 (RAG1, Accession NM\_000448) is another  
VGAM713 host target gene. RAG1 BINDING SITE is HOST  
TARGET binding site found in the 3` untranslated region  
of mRNA encoded by RAG1, corresponding to a HOST  
TARGET binding site such as BINDING SITE I, BINDING SITE  
II or BINDING SITE III. Table 2 illustrates the complemen-  
tarity of the nucleotide sequences of RAG1 BINDING SITE,  
designated SEQ ID:6041, to the nucleotide sequence of  
VGAM713 RNA, herein designated VGAM RNA, also desig-  
nated SEQ ID:3424.

[28653] Another function of VGAM713 is therefore inhibition of  
Recombination Activating Gene 1 (RAG1, Accession  
NM\_000448). Accordingly, utilities of VGAM713 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with RAG1. Sirtuin Silent Mating Type Information Regulation 2 Homolog 3 (*S. cerevisiae*) (SIRT3, Accession NM\_012239) is another VGAM713 host target gene. SIRT3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIRT3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIRT3 BINDING SITE, designated SEQ ID:14546, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28654] Another function of VGAM713 is therefore inhibition of Sirtuin Silent Mating Type Information Regulation 2 Homolog 3 (*S. cerevisiae*) (SIRT3, Accession NM\_012239), a gene which might function in telomeric silencing, cell cycle progression and chromosome stability. Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIRT3. The function of SIRT3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with

reference to VGAM140. Spondin 1, (f-spondin) Extracellular Matrix Protein (SPON1, Accession XM\_031184) is another VGAM713 host target gene. SPON1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPON1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPON1 BINDING SITE, designated SEQ ID:31305, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28655] Another function of VGAM713 is therefore inhibition of Spondin 1, (f-spondin) Extracellular Matrix Protein (SPON1, Accession XM\_031184). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPON1. Zinc Finger Protein 74 (Cos52) (ZNF74, Accession NM\_003426) is another VGAM713 host target gene. ZNF74 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF74, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of ZNF74 BINDING SITE, designated SEQ ID:9473, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28656] Another function of VGAM713 is therefore inhibition of Zinc Finger Protein 74 (Cos52) (ZNF74, Accession NM\_003426). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF74. Chromosome 21 Open Reading Frame 69 (C21orf69, Accession NM\_058189) is another VGAM713 host target gene. C21orf69 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C21orf69, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C21orf69 BINDING SITE, designated SEQ ID:27752, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28657] Another function of VGAM713 is therefore inhibition of Chromosome 21 Open Reading Frame 69 (C21orf69, Accession NM\_058189). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with C21orf69. Choline Kinase (CHK, Accession NM\_001277) is another VGAM713 host target gene. CHK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHK BINDING SITE, designated SEQ ID:6946, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28658] Another function of VGAM713 is therefore inhibition of Choline Kinase (CHK, Accession NM\_001277). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHK. DKFZP434N1235 (Accession NM\_031291) is another VGAM713 host target gene. DKFZP434N1235 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434N1235, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434N1235 BINDING SITE,

designated SEQ ID:25313, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28659] Another function of VGAM713 is therefore inhibition of DKFZP434N1235 (Accession NM\_031291). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434N1235. DKFZp547H025 (Accession NM\_020161) is another VGAM713 host target gene. DKFZp547H025 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547H025, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547H025 BINDING SITE, designated SEQ ID:21376, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28660] Another function of VGAM713 is therefore inhibition of DKFZp547H025 (Accession NM\_020161). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547H025. DRIL2 (Accession NM\_006465) is



another VGAM713 host target gene. DRIL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DRIL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRIL2 BINDING SITE, designated SEQ ID:13192, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28661] Another function of VGAM713 is therefore inhibition of DRIL2 (Accession NM\_006465). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRIL2. FLJ12294 (Accession NM\_025100) is another VGAM713 host target gene. FLJ12294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12294 BINDING SITE, designated SEQ ID:24745, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28662] Another function of VGAM713 is therefore inhibition of FLJ12294 (Accession NM\_025100). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12294. FLJ12476 (Accession NM\_022784) is another VGAM713 host target gene. FLJ12476 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ12476, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12476 BINDING SITE, designated SEQ ID:23068, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28663] Another function of VGAM713 is therefore inhibition of FLJ12476 (Accession NM\_022784). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12476. FLJ14525 (Accession NM\_032800) is another VGAM713 host target gene. FLJ14525 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14525, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14525 BINDING SITE, designated SEQ ID:26551, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28664] Another function of VGAM713 is therefore inhibition of FLJ14525 (Accession NM\_032800). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14525. FLJ20511 (Accession NM\_017853) is another VGAM713 host target gene. FLJ20511 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20511, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20511 BINDING SITE, designated SEQ ID:19528, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28665] Another function of VGAM713 is therefore inhibition of FLJ20511 (Accession NM\_017853). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20511.

FLJ23120 (Accession XM\_097961) is another VGAM713 host target gene. FLJ23120 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23120, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23120 BINDING SITE, designated SEQ ID:41264, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28666] Another function of VGAM713 is therefore inhibition of FLJ23120 (Accession XM\_097961). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23120. FLJ31951 (Accession NM\_144726) is another VGAM713 host target gene. FLJ31951 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ31951, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ31951 BINDING SITE, designated SEQ ID:29552, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3424.

[28667] Another function of VGAM713 is therefore inhibition of FLJ31951 (Accession NM\_144726). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ31951. KIAA0317 (Accession NM\_014821) is another VGAM713 host target gene. KIAA0317 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0317 BINDING SITE, designated SEQ ID:16798, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28668] Another function of VGAM713 is therefore inhibition of KIAA0317 (Accession NM\_014821). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0317. KIAA0321 (Accession XM\_031077) is another VGAM713 host target gene. KIAA0321 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0321, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0321 BINDING SITE, designated SEQ ID:31269, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28669] Another function of VGAM713 is therefore inhibition of KIAA0321 (Accession XM\_031077). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0321. KIAA0523 (Accession XM\_041964) is another VGAM713 host target gene. KIAA0523 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0523, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0523 BINDING SITE, designated SEQ ID:33647, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28670] Another function of VGAM713 is therefore inhibition of KIAA0523 (Accession XM\_041964). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0523. KIAA1598 (Accession NM\_018330) is another VGAM713 host target gene. KIAA1598 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1598, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1598 BINDING SITE, designated SEQ ID:20330, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28671] Another function of VGAM713 is therefore inhibition of KIAA1598 (Accession NM\_018330). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1598. KIAA1607 (Accession XM\_033379) is another VGAM713 host target gene. KIAA1607 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1607, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1607 BINDING SITE, designated SEQ ID:31914, to the

nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28672] Another function of VGAM713 is therefore inhibition of KIAA1607 (Accession XM\_033379). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1607. KIAA1911 (Accession XM\_056302) is another VGAM713 host target gene. KIAA1911 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1911, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1911 BINDING SITE, designated SEQ ID:36394, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28673] Another function of VGAM713 is therefore inhibition of KIAA1911 (Accession XM\_056302). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1911. MGC10818 (Accession NM\_030568) is another VGAM713 host target gene. MGC10818 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by MGC10818, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC10818 BINDING SITE, designated SEQ ID:24941, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28674] Another function of VGAM713 is therefore inhibition of MGC10818 (Accession NM\_030568). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10818. Monocyte to Macrophage Differentiation-associated (MMD, Accession XM\_008269) is another VGAM713 host target gene. MMD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MMD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MMD BINDING SITE, designated SEQ ID:30076, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28675] Another function of VGAM713 is therefore inhibition of

Monocyte to Macrophage Differentiation-associated (MMD, Accession XM\_008269). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MMD. RAP2B, Member of RAS Oncogene Family (RAP2B, Accession XM\_171061) is another VGAM713 host target gene. RAP2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAP2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAP2B BINDING SITE, designated SEQ ID:45862, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28676] Another function of VGAM713 is therefore inhibition of RAP2B, Member of RAS Oncogene Family (RAP2B, Accession XM\_171061). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAP2B. SEC15B (Accession XM\_039570) is another VGAM713 host target gene. SEC15B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

SEC15B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC15B BINDING SITE, designated SEQ ID:33130, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28677] Another function of VGAM713 is therefore inhibition of SEC15B (Accession XM\_039570). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEC15B. Tripartite Motif-containing 26 (TRIM26, Accession NM\_003449) is another VGAM713 host target gene. TRIM26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM26 BINDING SITE, designated SEQ ID:9500, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28678] Another function of VGAM713 is therefore inhibition of

Tripartite Motif-containing 26 (TRIM26, Accession NM\_003449). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM26. TU3A (Accession NM\_007177) is another VGAM713 host target gene. TU3A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TU3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TU3A BINDING SITE, designated SEQ ID:14037, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28679] Another function of VGAM713 is therefore inhibition of TU3A (Accession NM\_007177). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TU3A. ZER6 (Accession XM\_032742) is another VGAM713 host target gene. ZER6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZER6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of ZER6 BINDING SITE, designated SEQ ID:31743, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28680] Another function of VGAM713 is therefore inhibition of ZER6 (Accession XM\_032742). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZER6. Zinc Finger Protein 337 (ZNF337, Accession XM\_042807) is another VGAM713 host target gene. ZNF337 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF337 BINDING SITE, designated SEQ ID:33772, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28681] Another function of VGAM713 is therefore inhibition of Zinc Finger Protein 337 (ZNF337, Accession XM\_042807). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF337. LOC127702 (Accession

XM\_060619) is another VGAM713 host target gene.

LOC127702 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC127702, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127702 BINDING SITE, designated SEQ ID:37184, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28682] Another function of VGAM713 is therefore inhibition of LOC127702 (Accession XM\_060619). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127702. LOC146669 (Accession XM\_085534) is another VGAM713 host target gene. LOC146669 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146669, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146669 BINDING SITE, designated SEQ ID:38224, to the nucleotide sequence of VGAM713 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3424.

[28683] Another function of VGAM713 is therefore inhibition of LOC146669 (Accession XM\_085534). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146669. LOC146856 (Accession XM\_096086) is another VGAM713 host target gene. LOC146856 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146856, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146856 BINDING SITE, designated SEQ ID:40300, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28684] Another function of VGAM713 is therefore inhibition of LOC146856 (Accession XM\_096086). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146856. LOC150225 (Accession XM\_097870) is another VGAM713 host target gene. LOC150225 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150225, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150225 BINDING SITE, designated SEQ ID:41192, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28685] Another function of VGAM713 is therefore inhibition of LOC150225 (Accession XM\_097870). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150225. LOC150406 (Accession XM\_086908) is another VGAM713 host target gene. LOC150406 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150406, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150406 BINDING SITE, designated SEQ ID:38965, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28686] Another function of VGAM713 is therefore inhibition of LOC150406 (Accession XM\_086908). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with LOC150406. LOC152300 (Accession XM\_087432) is another VGAM713 host target gene. LOC152300 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152300, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152300 BINDING SITE, designated SEQ ID:39253, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28687] Another function of VGAM713 is therefore inhibition of LOC152300 (Accession XM\_087432). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152300. LOC154790 (Accession XM\_088044) is another VGAM713 host target gene. LOC154790 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154790, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154790 BINDING SITE, designated SEQ ID:39491, to

the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28688] Another function of VGAM713 is therefore inhibition of LOC154790 (Accession XM\_088044). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154790. LOC155081 (Accession XM\_088145) is another VGAM713 host target gene. LOC155081 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC155081, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155081 BINDING SITE, designated SEQ ID:39544, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28689] Another function of VGAM713 is therefore inhibition of LOC155081 (Accession XM\_088145). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155081. LOC170372 (Accession XM\_084317) is another VGAM713 host target gene. LOC170372 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC170372, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170372 BINDING SITE, designated SEQ ID:37540, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28690] Another function of VGAM713 is therefore inhibition of LOC170372 (Accession XM\_084317). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170372. LOC170425 (Accession XM\_084330) is another VGAM713 host target gene. LOC170425 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC170425, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170425 BINDING SITE, designated SEQ ID:37553, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28691] Another function of VGAM713 is therefore inhibition of LOC170425 (Accession XM\_084330). Accordingly, utilities

of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170425. LOC202802 (Accession XM\_114560) is another VGAM713 host target gene. LOC202802 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC202802, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202802 BINDING SITE, designated SEQ ID:42989, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28692] Another function of VGAM713 is therefore inhibition of LOC202802 (Accession XM\_114560). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202802. LOC221810 (Accession XM\_168222) is another VGAM713 host target gene. LOC221810 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221810, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC221810 BINDING SITE, designated SEQ ID:45086, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28693] Another function of VGAM713 is therefore inhibition of LOC221810 (Accession XM\_168222). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221810. LOC222228 (Accession XM\_168627) is another VGAM713 host target gene. LOC222228 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222228 BINDING SITE, designated SEQ ID:45275, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28694] Another function of VGAM713 is therefore inhibition of LOC222228 (Accession XM\_168627). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222228. LOC222233 (Accession XM\_168560) is another VGAM713 host target gene. LOC222233 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222233, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222233 BINDING SITE, designated SEQ ID:45244, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28695] Another function of VGAM713 is therefore inhibition of LOC222233 (Accession XM\_168560). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222233. LOC253502 (Accession XM\_170561) is another VGAM713 host target gene. LOC253502 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253502, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253502 BINDING SITE, designated SEQ ID:45381, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28696] Another function of VGAM713 is therefore inhibition of

LOC253502 (Accession XM\_170561). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253502. LOC255242 (Accession XM\_171095) is another VGAM713 host target gene. LOC255242 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255242, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255242 BINDING SITE, designated SEQ ID:45906, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28697] Another function of VGAM713 is therefore inhibition of LOC255242 (Accession XM\_171095). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255242. LOC257494 (Accession XM\_175212) is another VGAM713 host target gene. LOC257494 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257494, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC257494 BINDING SITE, designated SEQ ID:46687, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28698] Another function of VGAM713 is therefore inhibition of LOC257494 (Accession XM\_175212). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257494. LOC57115 (Accession NM\_020393) is another VGAM713 host target gene. LOC57115 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC57115, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57115 BINDING SITE, designated SEQ ID:21663, to the nucleotide sequence of VGAM713 RNA, herein designated VGAM RNA, also designated SEQ ID:3424.

[28699] Another function of VGAM713 is therefore inhibition of LOC57115 (Accession NM\_020393). Accordingly, utilities of VGAM713 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57115. Fig. 1 further provides a conceptual descrip-



tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 714 (VGAM714) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28700] VGAM714 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM714 was detected is described hereinabove with reference to Figs. 1–8.

[28701] VGAM714 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Herpesvirus 4. VGAM714 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28702] VGAM714 gene encodes a VGAM714 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM714 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM714 precursor RNA is designated SEQ ID:700, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:700 is

located at position 102811 relative to the genome of Bovine Herpesvirus 4.

[28703] VGAM714 precursor RNA folds onto itself, forming VGAM714 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28704] An enzyme complex designated DICER COMPLEX, `dices` the VGAM714 folded precursor RNA into VGAM714 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM714 RNA is designated SEQ ID:3425, and is provided hereinbelow with reference to the sequence listing part.

[28705] VGAM714 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM714 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM714 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[28706] VGAM714 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM714 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM714 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM714 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM714 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[28707] The complementary binding of VGAM714 RNA, herein designated VGAM RNA, to host target binding sites on VGAM714 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM714 host target RNA into VGAM714 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28708] It is appreciated that VGAM714 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM714 host target genes. The mRNA of each one of this plurality of VGAM714 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM714 RNA, herein designated VGAM RNA, and which when bound by VGAM714 RNA causes inhibition of translation of respective one or more VGAM714

host target proteins.

[28709] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM714 gene, herein designated VGAM GENE, on one or more VGAM714 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28710] It is yet further appreciated that a function of VGAM714 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of viral infection by Bovine Herpesvirus 4. Spe-

cific functions, and accordingly utilities, of VGAM714 correlate with, and may be deduced from, the identity of the host target genes which VGAM714 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28711] Nucleotide sequences of the VGAM714 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM714 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM714 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM714 are further described hereinbelow with reference to Table 1.

[28712] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM714 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM714 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28713] As mentioned hereinabove with reference to Fig. 1, a function of VGAM714 gene, herein designated VGAM is inhibition of expression of VGAM714 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM714 correlate with, and may be deduced from, the identity of the target genes which VGAM714 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28714] Insulin-like Growth Factor Binding Protein 3 (IGFBP3, Accession NM\_000598) is a VGAM714 host target gene. IGFBP3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IGFBP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IGFBP3 BINDING SITE, designated SEQ ID:6200, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28715] A function of VGAM714 is therefore inhibition of Insulin-like Growth Factor Binding Protein 3 (IGFBP3, Accession NM\_000598). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IGFBP3. Sulfotransferase Family, Cytosolic, 1C, Member 1 (SULT1C1, Accession NM\_001056) is another VGAM714 host target gene. SULT1C1 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by SULT1C1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SULT1C1 BINDING SITE, designated SEQ ID:6723, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28716] Another function of VGAM714 is therefore inhibition of Sulfotransferase Family, Cytosolic, 1C, Member 1 (SULT1C1, Accession NM\_001056). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SULT1C1. CGI-142 (Accession NM\_016073) is another VGAM714 host target gene. CGI-142 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CGI-142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CGI-142 BINDING SITE, designated SEQ ID:18148, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.



[28717] Another function of VGAM714 is therefore inhibition of CGI-142 (Accession NM\_016073). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CGI-142. FLJ20783 (Accession NM\_017958) is another VGAM714 host target gene. FLJ20783 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20783, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20783 BINDING SITE, designated SEQ ID:19669, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28718] Another function of VGAM714 is therefore inhibition of FLJ20783 (Accession NM\_017958). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20783. FLJ22625 (Accession NM\_024715) is another VGAM714 host target gene. FLJ22625 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22625, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

**BINDING SITE III.** Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22625 BINDING SITE, designated SEQ ID:24043, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28719] Another function of VGAM714 is therefore inhibition of FLJ22625 (Accession NM\_024715). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22625. KIAA1966 (Accession NM\_133370) is another VGAM714 host target gene. KIAA1966 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1966, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1966 BINDING SITE, designated SEQ ID:28495, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28720] Another function of VGAM714 is therefore inhibition of KIAA1966 (Accession NM\_133370). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1966. Lymphoid-restricted Membrane Protein (LRMP, Accession NM\_006152) is another VGAM714 host target gene. LRMP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LRMP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRMP BINDING SITE, designated SEQ ID:12806, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28721] Another function of VGAM714 is therefore inhibition of Lymphoid-restricted Membrane Protein (LRMP, Accession NM\_006152). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRMP. SV2 (Accession NM\_014849) is another VGAM714 host target gene. SV2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SV2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SV2 BINDING SITE, designated SEQ ID:16887, to the nucleotide sequence of VGAM714 RNA, herein designated

VGAM RNA, also designated SEQ ID:3425.

[28722] Another function of VGAM714 is therefore inhibition of SV2 (Accession NM\_014849). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SV2.

LOC152756 (Accession XM\_098262) is another VGAM714 host target gene. LOC152756 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152756, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152756 BINDING SITE, designated SEQ ID:41550, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28723] Another function of VGAM714 is therefore inhibition of LOC152756 (Accession XM\_098262). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152756. LOC84549 (Accession NM\_032509) is another VGAM714 host target gene. LOC84549 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC84549, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC84549 BINDING SITE, designated SEQ ID:26256, to the nucleotide sequence of VGAM714 RNA, herein designated VGAM RNA, also designated SEQ ID:3425.

[28724] Another function of VGAM714 is therefore inhibition of LOC84549 (Accession NM\_032509). Accordingly, utilities of VGAM714 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC84549. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 715 (VGAM715) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28725] VGAM715 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM715 was detected is described hereinabove with reference to Figs. 1–8.

[28726] VGAM715 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cercopithecine Her–

pesvirus 7. VGAM715 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28727] VGAM715 gene encodes a VGAM715 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM715 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM715 precursor RNA is designated SEQ ID:701, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:701 is located at position 36568 relative to the genome of Cercopithecine Herpesvirus 7.

[28728] VGAM715 precursor RNA folds onto itself, forming VGAM715 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28729] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM715 folded precursor RNA into VGAM715 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM715 RNA is designated SEQ ID:3426, and is provided hereinbelow with reference to the sequence listing part.

[28730] VGAM715 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM715 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM715 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28731] VGAM715 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM715 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM715 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM715 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM715 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28732] The complementary binding of VGAM715 RNA, herein designated VGAM RNA, to host target binding sites on VGAM715 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM715 host target RNA into VGAM715 host target protein, herein desig-



nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28733] It is appreciated that VGAM715 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM715 host target genes. The mRNA of each one of this plurality of VGAM715 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM715 RNA, herein designated VGAM RNA, and which when bound by VGAM715 RNA causes inhibition of translation of respective one or more VGAM715 host target proteins.

[28734] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM715 gene, herein designated VGAM GENE, on one or more VGAM715 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28735] It is yet further appreciated that a function of VGAM715 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM715 include diagnosis, prevention and treatment of viral infection by Cercopithecine Herpesvirus 7. Specific functions, and accordingly utilities, of VGAM715 correlate with, and may be deduced from, the identity of the host target genes which VGAM715 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28736] Nucleotide sequences of the VGAM715 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM715 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM715 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM715 are further described hereinbelow with reference to Table 1.

[28737] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM715 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM715 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28738] As mentioned hereinabove with reference to Fig. 1, a function of VGAM715 gene, herein designated VGAM is inhibition of expression of VGAM715 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM715 correlate with, and may be deduced from, the identity of the target genes which VGAM715 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28739] FLJ11259 (Accession NM\_018370) is a VGAM715 host target gene. FLJ11259 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11259, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11259 BINDING SITE, designated SEQ ID:20386, to the nucleotide sequence of VGAM715

RNA, herein designated VGAM RNA, also designated SEQ ID:3426.

[28740] A function of VGAM715 is therefore inhibition of FLJ11259 (Accession NM\_018370). Accordingly, utilities of VGAM715 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11259. MGC10946 (Accession NM\_030572) is another VGAM715 host target gene. MGC10946 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC10946, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC10946 BINDING SITE, designated SEQ ID:24946, to the nucleotide sequence of VGAM715 RNA, herein designated VGAM RNA, also designated SEQ ID:3426.

[28741] Another function of VGAM715 is therefore inhibition of MGC10946 (Accession NM\_030572). Accordingly, utilities of VGAM715 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10946. LOC149650 (Accession XM\_086623) is another VGAM715 host target gene. LOC149650 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC149650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149650 BINDING SITE, designated SEQ ID:38796, to the nucleotide sequence of VGAM715 RNA, herein designated VGAM RNA, also designated SEQ ID:3426.

[28742] Another function of VGAM715 is therefore inhibition of LOC149650 (Accession XM\_086623). Accordingly, utilities of VGAM715 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149650. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 716 (VGAM716) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28743] VGAM716 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM716 was detected is described hereinabove with reference to Figs. 1–8.

[28744] VGAM716 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Cercopithecine Herpesvirus 7. VGAM716 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28745] VGAM716 gene encodes a VGAM716 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM716 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM716 precursor RNA is designated SEQ ID:702, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:702 is located at position 34593 relative to the genome of Cercopithecine Herpesvirus 7.

[28746] VGAM716 precursor RNA folds onto itself, forming VGAM716 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28747] An enzyme complex designated DICER COMPLEX, `dices` the VGAM716 folded precursor RNA into VGAM716 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM716 RNA is designated SEQ ID:3427, and is provided hereinbelow with reference to the sequence listing part.

[28748] VGAM716 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM716 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM716 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28749] VGAM716 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM716 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM716 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM716 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM716 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[28750] The complementary binding of VGAM716 RNA, herein designated VGAM RNA, to host target binding sites on VGAM716 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM716 host tar-



get RNA into VGAM716 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28751] It is appreciated that VGAM716 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM716 host target genes. The mRNA of each one of this plurality of VGAM716 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM716 RNA, herein designated VGAM RNA, and which when bound by VGAM716 RNA causes inhibition of translation of respective one or more VGAM716 host target proteins.

[28752] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM716 gene, herein designated VGAM GENE, on one or more VGAM716 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28753] It is yet further appreciated that a function of VGAM716 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of viral infection by Cercopithecine Herpesvirus 7. Specific functions, and accordingly utilities, of VGAM716 correlate with, and may be deduced from, the identity of the host target genes which VGAM716 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28754] Nucleotide sequences of the VGAM716 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM716 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM716 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM716 are further

described hereinbelow with reference to Table 1.

[28755] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM716 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM716 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28756] As mentioned hereinabove with reference to Fig. 1, a function of VGAM716 gene, herein designated VGAM is inhibition of expression of VGAM716 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM716 correlate with, and may be deduced from, the identity of the target genes which VGAM716 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28757] POU Domain, Class 3, Transcription Factor 1 (POU3F1, Accession XM\_001334) is a VGAM716 host target gene. POU3F1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POU3F1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of POU3F1 BINDING SITE, designated SEQ ID:29830, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28758] A function of VGAM716 is therefore inhibition of POU Domain, Class 3, Transcription Factor 1 (POU3F1, Accession XM\_001334), a gene which involves in early embryogenesis and neurogenesis. Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POU3F1. The function of POU3F1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM85. Tropomodulin (TMOD, Accession NM\_003275) is another VGAM716 host target gene. TMOD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMOD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMOD BINDING SITE, designated SEQ ID:9293, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28759] Another function of VGAM716 is therefore inhibition of Tropomodulin (TMOD, Accession NM\_003275), a gene which blocks the elongation and depolymerization of the actin filaments at the pointed end. Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMOD. The function of TMOD has been established by previous studies. Tropomodulin is associated with the pointed end of the actin filaments (Fowler et al., 1993). It binds specifically to the N terminus of tropomyosin and blocks the elongation and depolarization of tropomyosin-coated actin filaments. By Northern blot analysis, Sung et al. (1996) showed that the TMOD gene is expressed in major human tissues at different levels in the following order: heart and skeletal muscle much greater than in brain, lung, and pancreas, which is greater than in placenta, liver, and kidney. They pointed to structural similarities between tropomodulin and the 64-kD autoantigen in Graves disease (OMIM Ref. No. 139080) and suggested that the 2 genes evolved from a common ancestral gene. Chu et al. (2000) noted that erythrocyte TMOD is a 359-amino acid globular protein. Using PCR methods to obtain TMOD genomic clones, they determined that the

TMOD gene contains 9 exons. Chu et al. (2000) suggested that the use of alternative promoters may account for tissue-specific expression and regulation.

[28760] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28761] Fowler, V. M.; Sussmann, M. A.; Miller, P. G.; Flucher, B. E.; Daniels, M. P. : Tropomodulin is associated with the free (pointed) ends of the thin filaments in rat skeletal muscle. J. Cell Biol. 120: 411–420, 1993. ; and

[28762] Chu, X.; Thompson, D.; Yee, L. J.; Sung, L. A. : Genomic organization of mouse and human erythrocyte tropomodulin genes encoding the pointed end capping protein for the actin filaments.

[28763] Further studies establishing the function and utilities of TMOD are found in John Hopkins OMIM database record ID 190930, and in cited publications numbered 3262–3265, 80 and 3266–3270 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger Protein 80 (pT17) (ZNF80, Accession NM\_007136) is another VGAM716 host target gene. ZNF80 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ZNF80,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF80 BINDING SITE, designated SEQ ID:13987, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28764] Another function of VGAM716 is therefore inhibition of Zinc Finger Protein 80 (pT17) (ZNF80, Accession NM\_007136). Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF80. Lysyl Oxidase-like 4 (LOXL4, Accession NM\_032211) is another VGAM716 host target gene. LOXL4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOXL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOXL4 BINDING SITE, designated SEQ ID:25927, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28765] Another function of VGAM716 is therefore inhibition of

Lysyl Oxidase-like 4 (LOXL4, Accession NM\_032211). Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOXL4. Sideroflexin 2 (SFXN2, Accession XM\_058359) is another VGAM716 host target gene. SFXN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFXN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFXN2 BINDING SITE, designated SEQ ID:36605, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28766] Another function of VGAM716 is therefore inhibition of Sideroflexin 2 (SFXN2, Accession XM\_058359). Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFXN2. LOC145814 (Accession XM\_085243) is another VGAM716 host target gene. LOC145814 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145814, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-



illustrates the complementarity of the nucleotide sequences of LOC145814 BINDING SITE, designated SEQ ID:37986, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28767] Another function of VGAM716 is therefore inhibition of LOC145814 (Accession XM\_085243). Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145814. LOC147042 (Accession XM\_097167) is another VGAM716 host target gene. LOC147042 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147042, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147042 BINDING SITE, designated SEQ ID:40786, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28768] Another function of VGAM716 is therefore inhibition of LOC147042 (Accession XM\_097167). Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147042. LOC196540 (Accession XM\_116933) is an-

other VGAM716 host target gene. LOC196540 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196540, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196540 BINDING SITE, designated SEQ ID:43149, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28769] Another function of VGAM716 is therefore inhibition of LOC196540 (Accession XM\_116933). Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196540. LOC51141 (Accession XM\_043953) is another VGAM716 host target gene. LOC51141 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51141, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51141 BINDING SITE, designated SEQ ID:34046, to the nucleotide sequence of VGAM716 RNA, herein designated VGAM RNA, also designated SEQ ID:3427.

[28770] Another function of VGAM716 is therefore inhibition of LOC51141 (Accession XM\_043953). Accordingly, utilities of VGAM716 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51141. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 717 (VGAM717) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28771] VGAM717 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM717 was detected is described hereinabove with reference to Figs. 1–8.

[28772] VGAM717 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cercopithecine Herpesvirus 7. VGAM717 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28773] VGAM717 gene encodes a VGAM717 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM717

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM717 precursor RNA is designated SEQ ID:703, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:703 is located at position 37440 relative to the genome of Cercopithecine Herpesvirus 7.

[28774] VGAM717 precursor RNA folds onto itself, forming VGAM717 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28775] An enzyme complex designated DICER COMPLEX, `dices` the VGAM717 folded precursor RNA into VGAM717 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 79%) nucleotide sequence of VGAM717 RNA is designated SEQ ID:3428, and is provided hereinbelow with reference to the sequence listing part.

[28776] VGAM717 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM717 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM717 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[28777] VGAM717 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM717 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM717 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM717 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM717 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28778] The complementary binding of VGAM717 RNA, herein designated VGAM RNA, to host target binding sites on VGAM717 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM717 host target RNA into VGAM717 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28779] It is appreciated that VGAM717 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM717 host target genes. The mRNA of each one of this plurality of VGAM717 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM717 RNA, herein designated VGAM RNA, and which when bound by VGAM717 RNA causes inhibition of translation of respective one or more VGAM717 host target proteins.

[28780] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM717 gene, herein designated VGAM GENE, on one or more VGAM717 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28781] It is yet further appreciated that a function of VGAM717 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM717 include diagnosis, prevention and treatment of viral infection by Cercopithecine Herpesvirus 7. Specific functions, and accordingly utilities, of VGAM717 correlate with, and may be deduced from, the identity of the host target genes which VGAM717 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28782] Nucleotide sequences of the VGAM717 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM717 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM717 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM717 are further described hereinbelow with reference to Table 1.

[28783] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM717 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM717 RNA, herein designated VGAM RNA, are described hereinbelow with refer-



ence to Table 2.

[28784] As mentioned hereinabove with reference to Fig. 1, a function of VGAM717 gene, herein designated VGAM is inhibition of expression of VGAM717 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM717 correlate with, and may be deduced from, the identity of the target genes which VGAM717 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28785] B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633) is a VGAM717 host target gene. BCL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2 BINDING SITE, designated SEQ ID:6255, to the nucleotide sequence of VGAM717 RNA, herein designated VGAM RNA, also designated SEQ ID:3428.

[28786] A function of VGAM717 is therefore inhibition of B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633). Accordingly, utilities of VGAM717 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with BCL2. LOC120939 (Accession XM\_073688) is another VGAM717 host target gene. LOC120939 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120939, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120939 BINDING SITE, designated SEQ ID:37515, to the nucleotide sequence of VGAM717 RNA, herein designated VGAM RNA, also designated SEQ ID:3428.

[28787] Another function of VGAM717 is therefore inhibition of LOC120939 (Accession XM\_073688). Accordingly, utilities of VGAM717 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120939. LOC143381 (Accession XM\_084501) is another VGAM717 host target gene. LOC143381 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143381, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143381 BINDING SITE, designated SEQ ID:37612, to the nucleotide sequence of VGAM717 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3428.

[28788] Another function of VGAM717 is therefore inhibition of LOC143381 (Accession XM\_084501). Accordingly, utilities of VGAM717 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143381. LOC257095 (Accession XM\_173058) is another VGAM717 host target gene. LOC257095 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257095, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257095 BINDING SITE, designated SEQ ID:46312, to the nucleotide sequence of VGAM717 RNA, herein designated VGAM RNA, also designated SEQ ID:3428.

[28789] Another function of VGAM717 is therefore inhibition of LOC257095 (Accession XM\_173058). Accordingly, utilities of VGAM717 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257095. LOC51055 (Accession NM\_015901) is another VGAM717 host target gene. LOC51055 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51055, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51055 BINDING SITE, designated SEQ ID:18044, to the nucleotide sequence of VGAM717 RNA, herein designated VGAM RNA, also designated SEQ ID:3428.

[28790] Another function of VGAM717 is therefore inhibition of LOC51055 (Accession NM\_015901). Accordingly, utilities of VGAM717 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51055. LOC92597 (Accession XM\_046066) is another VGAM717 host target gene. LOC92597 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92597, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92597 BINDING SITE, designated SEQ ID:34673, to the nucleotide sequence of VGAM717 RNA, herein designated VGAM RNA, also designated SEQ ID:3428.

[28791] Another function of VGAM717 is therefore inhibition of LOC92597 (Accession XM\_046066). Accordingly, utilities of VGAM717 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC92597. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 718 (VGAM718) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28792] VGAM718 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM718 was detected is described hereinabove with reference to Figs. 1–8.

[28793] VGAM718 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cercopithecine Herpesvirus 7. VGAM718 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28794] VGAM718 gene encodes a VGAM718 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM718 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM718 precursor RNA is designated SEQ

ID:704, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:704 is located at position 39450 relative to the genome of Cercopithecine Herpesvirus 7.

[28795] VGAM718 precursor RNA folds onto itself, forming VGAM718 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28796] An enzyme complex designated DICER COMPLEX, `dices` the VGAM718 folded precursor RNA into VGAM718 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 64%) nucleotide sequence of VGAM718 RNA is designated SEQ ID:3429, and is provided hereinbelow with reference to the sequence

listing part.

[28797] VGAM718 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM718 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM718 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28798] VGAM718 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM718 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM718 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM718 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM718 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28799] The complementary binding of VGAM718 RNA, herein designated VGAM RNA, to host target binding sites on VGAM718 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM718 host target RNA into VGAM718 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28800] It is appreciated that VGAM718 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM718 host target genes. The mRNA of each one of this plurality of VGAM718 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM718 RNA, herein designated VGAM



RNA, and which when bound by VGAM718 RNA causes inhibition of translation of respective one or more VGAM718 host target proteins.

[28801] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM718 gene, herein designated VGAM GENE, on one or more VGAM718 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28802] It is yet further appreciated that a function of VGAM718 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM718 include diagnosis, prevention and treatment of viral infection by Cercopithecine Herpesvirus 7. Specific functions, and accordingly utilities, of VGAM718 correlate with, and may be deduced from, the identity of the host target genes which VGAM718 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28803] Nucleotide sequences of the VGAM718 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM718 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM718 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM718 are further described hereinbelow with reference to Table 1.

[28804] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM718 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM718 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28805] As mentioned hereinabove with reference to Fig. 1, a function of VGAM718 gene, herein designated VGAM is

inhibition of expression of VGAM718 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM718 correlate with, and may be deduced from, the identity of the target genes which VGAM718 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28806] Fibrinogen, A Alpha Polypeptide (FGA, Accession NM\_000508) is a VGAM718 host target gene. FGA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FGA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGA BINDING SITE, designated SEQ ID:6118, to the nucleotide sequence of VGAM718 RNA, herein designated VGAM RNA, also designated SEQ ID:3429.

[28807] A function of VGAM718 is therefore inhibition of Fibrinogen, A Alpha Polypeptide (FGA, Accession NM\_000508). Accordingly, utilities of VGAM718 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGA. Pleiomorphic Adenoma Gene-like 2 (PLAGL2, Accession XM\_047007) is another VGAM718 host target gene. PLAGL2 BINDING SITE is HOST TARGET

binding site found in the 3` untranslated region of mRNA encoded by PLAGL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLAGL2 BINDING SITE, designated SEQ ID:34872, to the nucleotide sequence of VGAM718 RNA, herein designated VGAM RNA, also designated SEQ ID:3429.

[28808] Another function of VGAM718 is therefore inhibition of Pleiomorphic Adenoma Gene-like 2 (PLAGL2, Accession XM\_047007). Accordingly, utilities of VGAM718 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLAGL2. LOC256112 (Accession XM\_172829) is another VGAM718 host target gene. LOC256112 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC256112, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256112 BINDING SITE, designated SEQ ID:46101, to the nucleotide sequence of VGAM718 RNA, herein designated VGAM RNA, also designated SEQ ID:3429.

[28809] Another function of VGAM718 is therefore inhibition of LOC256112 (Accession XM\_172829). Accordingly, utilities of VGAM718 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256112. LOC92979 (Accession NM\_138396) is another VGAM718 host target gene. LOC92979 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92979, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92979 BINDING SITE, designated SEQ ID:28765, to the nucleotide sequence of VGAM718 RNA, herein designated VGAM RNA, also designated SEQ ID:3429.

[28810] Another function of VGAM718 is therefore inhibition of LOC92979 (Accession NM\_138396). Accordingly, utilities of VGAM718 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92979. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 719 (VGAM719) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[28811] VGAM719 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM719 was detected is described hereinabove with reference to Figs. 1–8.

[28812] VGAM719 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ectocarpus Siliculosus Virus. VGAM719 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28813] VGAM719 gene encodes a VGAM719 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM719 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM719 precursor RNA is designated SEQ ID:705, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:705 is located at position 32262 relative to the genome of Ectocarpus Siliculosus Virus.

[28814] VGAM719 precursor RNA folds onto itself, forming VGAM719 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[28815] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM719 folded precursor RNA into VGAM719 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 44%) nucleotide se-  
quence of VGAM719 RNA is designated SEQ ID:3430, and  
is provided hereinbelow with reference to the sequence  
listing part.

[28816] VGAM719 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM719 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM719 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28817] VGAM719 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM719 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM719 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM719 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM719 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in



the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28818] The complementary binding of VGAM719 RNA, herein designated VGAM RNA, to host target binding sites on VGAM719 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM719 host target RNA into VGAM719 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28819] It is appreciated that VGAM719 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM719 host target genes. The mRNA of each one of this plurality of VGAM719 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM719 RNA, herein designated VGAM RNA, and which when bound by VGAM719 RNA causes inhibition of translation of respective one or more VGAM719 host target proteins.

[28820] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM719 gene, herein designated VGAM GENE, on one or more VGAM719 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28821] It is yet further appreciated that a function of VGAM719 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM719 include diagnosis, prevention and treatment of viral infection by Ectocarpus Siliculosus Virus. Specific functions, and accordingly utilities, of VGAM719 correlate with, and may be deduced from, the identity of the host target genes which VGAM719 binds and inhibits, and the function of these host target genes,

as elaborated hereinbelow.

[28822] Nucleotide sequences of the VGAM719 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM719 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM719 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM719 are further described hereinbelow with reference to Table 1.

[28823] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM719 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM719 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28824] As mentioned hereinabove with reference to Fig. 1, a function of VGAM719 gene, herein designated VGAM is inhibition of expression of VGAM719 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM719 correlate with, and may be deduced from, the identity of the target genes which VGAM719 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28825] Fibroblast Growth Factor 4 (heparin secretory transforming protein 1, Kaposi sarcoma oncogene) (FGF4, Accession NM\_002007) is a VGAM719 host target gene. FGF4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FGF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF4 BINDING SITE, designated SEQ ID:7745, to the nucleotide sequence of VGAM719 RNA, herein designated VGAM RNA, also designated SEQ ID:3430.

[28826] A function of VGAM719 is therefore inhibition of Fibroblast Growth Factor 4 (heparin secretory transforming protein 1, Kaposi sarcoma oncogene) (FGF4, Accession NM\_002007), a gene which can transform nih 3t3 cells from a human stomach tumor (hst) and from kaposi's sarcoma (ks3). Accordingly, utilities of VGAM719 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF4. The function of FGF4 has been established by previous studies. Sakamoto et al. (1986) tested the capacity for malignant transformation of DNA from 21 stomach cancers, 16 stomach cancers metastatic to lymph nodes, and 21 specimens of appar-

ently noncancerous stomach mucosa from a total of 26 patients with stomach cancer. The DNA was transferred to NIH 3T3 cells by the calcium precipitation technique. Transforming ability was shown by 3 samples: a primary cancer, a metastatic cancer, and a presumably normal gastric mucosa. The transforming gene from the primary cancer was cloned. It bore no homology with previously reported transforming sequences. Taira et al. (1987) isolated an HST cDNA clone that had an efficient transforming activity in a focus-forming assay when it was inserted into an expression vector. Characterization of this clone allowed Taira et al. (1987) to predict that a 206-amino acid protein product was responsible for this transforming activity. In an addendum, Taira et al. (1987) indicated that 42.3% homology existed between the amino acid residues of 1 ORF (open reading frame) of HST and part of bovine basic fibroblast growth factor. They suggested that further studies would elucidate the role of the HST gene in the development of stomach cancer which, they stated, has the highest incidence of all known cancers. By in situ hybridization, Adelaide et al. (1988) mapped the HST gene to chromosome 11q13. This is also the location of the INT2 gene. Furthermore, Adelaide et al. (1988) found the

2 genes to be coamplified in a human melanoma. Huebner et al. (1988) mapped the K-FGF oncogene to 11q11-q23 by hybridization studies using DNA from rodent-human somatic cell hybrids and then localized it more precisely to 11q13 by in situ hybridization. The 11q13 region is also the site of the BCL1 gene (OMIM Ref. No. 168461), which is involved in the 11;14 translocation characteristic of some B-cell tumors; see 151400. The oncogene SEA (OMIM Ref. No. 165110) has also been mapped to 11q13. By pulsed-field gel electrophoresis and by analysis of overlapping cosmid clones, Wada et al. (1988) concluded that HST1 is located about 35 kb downstream of INT2 in the same transcriptional orientation. Animal model experiments lend further support to the function of FGF4. Feldman et al. (1995) demonstrated that Fgf4  $-/-$  embryos die on embryonic day 5.0. To circumvent this early lethality and assess Fgf4 function in limb development, Sun et al. (2000) used the Cre/loxP system and found that Shh expression is maintained and limb formation is normal when Fgf4 is inactivated in mouse limbs, contradicting another model which suggested that Fgf4 expression is not maintained in Shh  $-/-$  mouse limbs. Sun et al. (2000) also found that maintenance of Fgf9 (OMIM Ref. No. 600921)

and Fgf17 (OMIM Ref. No. 603725) expression is dependent on Shh, whereas Fgf8 (OMIM Ref. No. 600483) expression is not. Sun et al. (2000) developed a model in which no individual Fgf expressed in the apical ectodermal ridge is solely necessary to maintain Shh expression, but instead the combined activity of 2 or more apical ectodermal ridge Fgfs function in a positive feedback loop with Shh to control limb development.

[28827] It is appreciated that the abovementioned animal model for FGF4 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[28828] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28829] Taira, M.; Yoshida, T.; Miyagawa, K.; Sakamoto, H.; Terada, M.; Sugimura, T. : cDNA sequence of human transforming gene hst and identification of the coding sequence required for transforming activity. Proc. Nat. Acad. Sci. 84: 2980–2984, 1987. ; and

[28830] Huebner, K.; Ferrari, A. C.; Delli Bovi, P.; Croce, C. M.; Basilico, C. : The FGF-related oncogene, K-FGF, maps to human chromosome region 11q13, possibly near int-2.

Oncogene Res. 3: 26.

[28831] Further studies establishing the function and utilities of FGF4 are found in John Hopkins OMIM database record ID 164980, and in cited publications numbered 3284–3287, 2604, 3288–3290, 11445, 11531–1153 and 2130 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Natriuretic Peptide Receptor A/guanylate Cyclase A (atrionatriuretic peptide receptor A) (NPR1, Accession XM\_113360) is another VGAM719 host target gene. NPR1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NPR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NPR1 BINDING SITE, designated SEQ ID:42233, to the nucleotide sequence of VGAM719 RNA, herein designated VGAM RNA, also designated SEQ ID:3430.

[28832] Another function of VGAM719 is therefore inhibition of Natriuretic Peptide Receptor A/guanylate Cyclase A (atrionatriuretic peptide receptor A) (NPR1, Accession XM\_113360), a gene which has guanylate cyclase activity on binding of anp. Accordingly, utilities of VGAM719 in-



clude diagnosis, prevention and treatment of diseases and clinical conditions associated with NPR1. The function of NPR1 has been established by previous studies. The precursor of atrial natriuretic peptide (ANP; 108780) is produced and stored mainly in the right atrium of the heart (see OMIM Ref. No. Oliver et al., 1997). ANP formed from this precursor is released in response to atrial stretch. Once in the circulation, ANP binds to the natriuretic peptide receptor A (ANPRA, or NPR1), also known as guanylate cyclase A (or GC-A), mainly in the kidney, vascular tissue, and adrenal gland. This binding induces an increase in intracellular cGMP and initiates natriuresis, diuresis, and vasodilation, all of which contribute to lowering blood pressure. 'B-type' natriuretic peptide, a structurally related peptide formed mainly in the cardiac ventricles, also acts through ANPRA and has effects similar to ANP. Lowe et al. (1990) assigned the ANPRA gene to 1q12-qter by PCR analysis of genomic DNA from somatic cell hybrids. By in situ hybridization, the gene was further localized to 1q21-q22. Animal model experiments lend further support to the function of NPR1. To study the role of NPRA in the regulation of blood pressure and in the cardiovascular response to sustained hypertension, Oliver

et al. (1997) made mice completely lacking this receptor. They found that mice lacking a functional Npr1 gene coding for NPRA had elevated blood pressures and heart exhibiting marked hypertrophy with interstitial fibrosis resembling that seen in human hypertensive heart disease. Echocardiographic evaluation of the mice demonstrated a compensated state of systemic hypertension in which cardiac hypertrophy and dilatation were evident but with no reduction in ventricular performance. Nevertheless, sudden death, with morphologic evidence indicative in some animals of congestive heart failure and in others of aortic dissection, occurred in all 15 male mice lacking Npr1 before 6 months of age, and in 1 of 16 females in this study.

[28833] It is appreciated that the abovementioned animal model for NPR1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[28834] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28835] Lowe, D. G.; Klisak, I.; Sparkes, R. S.; Mohandas, T.; Goedel, D. V. : Chromosomal distribution of three members of the human natriuretic peptide receptor/guanylyl cyclase

gene family. Genomics 8: 304–312, 1990. ; and

[28836] Oliver, P. M.; Fox, J. E.; Kim, R.; Rockman, H. A.; Kim, H.-S.; Reddick, R. L.; Pandey, K. N.; Milgram, S. L.; Smithies, O.; Maeda, N. : Hypertension, cardiac hypertrophy, and sudden dea.

[28837] Further studies establishing the function and utilities of NPR1 are found in John Hopkins OMIM database record ID 108960, and in cited publications numbered 4235–423 and 4318–4319 listed in the bibliography section herein–below, which are also hereby incorporated by reference. T-box, Brain, 1 (TBR1, Accession NM\_006593) is another VGAM719 host target gene. TBR1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TBR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBR1 BINDING SITE, designated SEQ ID:13357, to the nucleotide sequence of VGAM719 RNA, herein designated VGAM RNA, also designated SEQ ID:3430.

[28838] Another function of VGAM719 is therefore inhibition of T-box, Brain, 1 (TBR1, Accession NM\_006593), a gene which is of unknown function. Accordingly, utilities of VGAM719

include diagnosis, prevention and treatment of diseases and clinical conditions associated with TBR1. The function of TBR1 has been established by previous studies. Using subtractive hybridization of day 14.5 embryonic telencephalon and adult telencephalon, Bulfone et al. (1995) identified a mouse cDNA for Tbr1 (T-brain-1). Using mouse Tbr1 as a probe to screen a week 17 human fetal cDNA library, the authors identified a TBR1 cDNA encoding a 682-amino acid protein. The sequence of the TBR1 protein is 99% identical to the mouse sequence; both show high homology, particularly in the T-box DNA-binding domain, with the protein product of the T (Brachyury) gene (see OMIM Ref. No. 601397). Northern blot and in situ hybridization analyses revealed that expression of mouse Tbr1 is largely restricted to the cerebral cortex. It is expressed in postmitotic cells in the forebrain with onset during embryogenesis and continues to be expressed in the adult brain. Expression is 10-fold more abundant in embryonic than in adult tissue. To identify binding partners for the guanylate kinase domain of CASK (OMIM Ref. No. 300172), Hsueh et al. (2000) carried out a yeast 2-hybrid screen of brain cDNA libraries, from which TBR1 was isolated. By deletion analysis, the C-

terminal region of TBR1 (residues 342 to 681) was found to be necessary and sufficient for association with the guanylate kinase domain of CASK. When coexpressed in COS-7 cells, TBR1 and CASK were readily coprecipitated by antibodies directed against either individual protein. Hsueh et al. (2000) demonstrated that CASK enters the nucleus and binds to a specific DNA sequence (the T element) in a complex with TBR1. CASK acts as a coactivator of TBR1 to induce transcription of T element-containing genes, including reelin, a gene that is essential for cerebrocortical development.

[28839] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28840] Bulfone, A.; Smiga, S. M.; Shimamura, K.; Peterson, A.; Puelles, L.; Rubenstein, J. L. R. : T-brain-1: a homolog of Brachyury whose expression defines molecularly distinct domains within the cerebral cortex. *Neuron* 15: 63-78, 1995. ; and

[28841] Hsueh, Y.-P.; Wang, T.-F.; Yang, F.-C.; Sheng, M. : Nuclear transcription and transcription regulation by the membrane-associated guanylate kinase CASK/LIN-2. *Nature* 404: 298-302, 2000.

[28842] Further studies establishing the function and utilities of TBR1 are found in John Hopkins OMIM database record ID 604616, and in cited publications numbered 504 and 7047 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0125 (Accession XM\_018203) is another VGAM719 host target gene. KIAA0125 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0125, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0125 BINDING SITE, designated SEQ ID:30342, to the nucleotide sequence of VGAM719 RNA, herein designated VGAM RNA, also designated SEQ ID:3430.

[28843] Another function of VGAM719 is therefore inhibition of KIAA0125 (Accession XM\_018203). Accordingly, utilities of VGAM719 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0125. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 720 (VGAM720) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28844] VGAM720 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM720 was detected is described hereinabove with reference to Figs. 1–8.

[28845] VGAM720 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ectocarpus Siliculosus Virus. VGAM720 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28846] VGAM720 gene encodes a VGAM720 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM720 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM720 precursor RNA is designated SEQ ID:706, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:706 is located at position 33937 relative to the genome of Ectocarpus Siliculosus Virus.

[28847] VGAM720 precursor RNA folds onto itself, forming

VGAM720 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28848] An enzyme complex designated DICER COMPLEX, `dices` the VGAM720 folded precursor RNA into VGAM720 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM720 RNA is designated SEQ ID:3431, and is provided hereinbelow with reference to the sequence listing part.

[28849] VGAM720 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM720 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM720 host target RNA comprises



three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28850] VGAM720 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM720 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM720 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM720 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM720 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28851] The complementary binding of VGAM720 RNA, herein designated VGAM RNA, to host target binding sites on VGAM720 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM720 host target RNA into VGAM720 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28852] It is appreciated that VGAM720 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM720 host target genes. The mRNA of each one of this plurality of VGAM720 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM720 RNA, herein designated VGAM RNA, and which when bound by VGAM720 RNA causes inhibition of translation of respective one or more VGAM720 host target proteins.

[28853] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM720 gene, herein designated VGAM GENE, on one or more VGAM720 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28854] It is yet further appreciated that a function of VGAM720 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM720 include diagnosis, prevention and treatment of viral infection by Ectocarpus Siliculosus Virus. Specific functions, and accordingly utilities, of VGAM720 correlate with, and may be deduced from, the identity of the host target genes which VGAM720 binds

and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28855] Nucleotide sequences of the VGAM720 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM720 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM720 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM720 are further described hereinbelow with reference to Table 1.

[28856] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM720 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM720 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28857] As mentioned hereinabove with reference to Fig. 1, a function of VGAM720 gene, herein designated VGAM is inhibition of expression of VGAM720 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM720 correlate with, and may be deduced from, the identity of the target genes which VGAM720 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[28858] MLL Septin-like Fusion (MSF, Accession XM\_113892) is a VGAM720 host target gene. MSF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSF BINDING SITE, designated SEQ ID:42520, to the nucleotide sequence of VGAM720 RNA, herein designated VGAM RNA, also designated SEQ ID:3431.

[28859] A function of VGAM720 is therefore inhibition of MLL Septin-like Fusion (MSF, Accession XM\_113892), a gene which plays a role in the cell cycle. Accordingly, utilities of VGAM720 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSF. The function of MSF and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM514. Carbohydrate (N-acetylgalactosamine 4-O) Sulfotransferase 8 (CHST8, Accession NM\_022467) is another VGAM720 host target gene. CHST8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region

of mRNA encoded by CHST8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST8 BINDING SITE, designated SEQ ID:22817, to the nucleotide sequence of VGAM720 RNA, herein designated VGAM RNA, also designated SEQ ID:3431.

[28860] Another function of VGAM720 is therefore inhibition of Carbohydrate (N-acetylgalactosamine 4-0) Sulfotransferase 8 (CHST8, Accession NM\_022467). Accordingly, utilities of VGAM720 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHST8. KIAA0435 (Accession NM\_014801) is another VGAM720 host target gene. KIAA0435 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0435, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0435 BINDING SITE, designated SEQ ID:16718, to the nucleotide sequence of VGAM720 RNA, herein designated VGAM RNA, also designated SEQ ID:3431.

[28861] Another function of VGAM720 is therefore inhibition of

KIAA0435 (Accession NM\_014801). Accordingly, utilities of VGAM720 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0435. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 721 (VGAM721) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28862] VGAM721 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM721 was detected is described hereinabove with reference to Figs. 1–8.

[28863] VGAM721 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Mosaic Virus. VGAM721 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28864] VGAM721 gene encodes a VGAM721 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM721 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM721 precursor RNA is designated SEQ ID:707, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:707 is located at position 1715 relative to the genome of Tomato Mosaic Virus.

[28865] VGAM721 precursor RNA folds onto itself, forming VGAM721 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28866] An enzyme complex designated DICER COMPLEX, `dices` the VGAM721 folded precursor RNA into VGAM721 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide se-



quence of VGAM721 RNA is designated SEQ ID:3432, and is provided hereinbelow with reference to the sequence listing part.

[28867] VGAM721 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM721 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM721 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[28868] VGAM721 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM721 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM721 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM721 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM721 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[28869] The complementary binding of VGAM721 RNA, herein designated VGAM RNA, to host target binding sites on VGAM721 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM721 host target RNA into VGAM721 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28870] It is appreciated that VGAM721 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM721 host target genes. The mRNA of each one of this plurality of VGAM721 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM721 RNA, herein designated VGAM RNA, and which when bound by VGAM721 RNA causes inhibition of translation of respective one or more VGAM721 host target proteins.

[28871] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM721 gene, herein designated VGAM GENE, on one or more VGAM721 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28872] It is yet further appreciated that a function of VGAM721 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of viral infection by Tomato Mosaic Virus. Specific functions, and accordingly utilities, of VGAM721 correlate with, and may be deduced from, the identity of the host target genes which VGAM721 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28873] Nucleotide sequences of the VGAM721 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM721 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM721 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM721 are further described hereinbelow with reference to Table 1.

[28874] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM721 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM721 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28875] As mentioned hereinabove with reference to Fig. 1, a function of VGAM721 gene, herein designated VGAM is inhibition of expression of VGAM721 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM721 correlate with, and may be deduced from, the identity of the target genes which VGAM721 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28876] DNA (cytosine-5-)-methyltransferase 3 Beta (DNMT3B, Accession NM\_006892) is a VGAM721 host target gene. DNMT3B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DNMT3B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNMT3B BINDING SITE, designated SEQ ID:13758, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28877] A function of VGAM721 is therefore inhibition of DNA (cytosine-5-)-methyltransferase 3 Beta (DNMT3B, Accession NM\_006892), a gene which is required for genome wide de novo methylation. Accordingly, utilities of

VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNMT3B. The function of DNMT3B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM280. Oxidation Resistance 1 (OXR1, Accession NM\_018002) is another VGAM721 host target gene. OXR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OXR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OXR1 BINDING SITE, designated SEQ ID:19731, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28878] Another function of VGAM721 is therefore inhibition of Oxidation Resistance 1 (OXR1, Accession NM\_018002). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OXR1. V-src Sarcoma (Schmidt-Ruppin A-2) Viral Oncogene Homolog (avian) (SRC, Accession NM\_005417) is another VGAM721 host target gene. SRC BINDING SITE is HOST TARGET binding site found in the

3' untranslated region of mRNA encoded by SRC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRC BINDING SITE, designated SEQ ID:11886, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28879] Another function of VGAM721 is therefore inhibition of V-src Sarcoma (Schmidt-Ruppin A-2) Viral Oncogene Homolog (avian) (SRC, Accession NM\_005417), a gene which is a tyrosine kinase. Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRC. The function of SRC has been established by previous studies. Elevated c-src tyrosine kinase activity has been found in colon cancers, particularly in those metastatic to the liver. Studies of the mechanism of SRC regulation suggested that SRC kinase activity is downregulated by phosphorylation of a critical C-terminal tyrosine (tyr530 in human SRC, equivalent to tyr527 in chicken Src) and have implied the existence of activating mutations in this C-terminal regulatory region. Irby et al. (1999) reported the identification of a truncating mutation in SRC at codon 531 in 12% of cases

of advanced human colon cancer tested and demonstrated that the mutation is activating, transforming, tumorigenic, and metastasis-promoting. The results provided, for the first time, genetic evidence that activating SRC mutations may have a role in the malignant progression of human colon cancer. SRC is the symbol for the human gene homologous in sequence to the v-src gene of the Rous sarcoma virus (also called avian sarcoma virus, ASV). The human protooncogene was assigned to chromosome 20 by somatic cell hybrid studies (Sakaguchi et al., 1982). Le Beau et al. (1984) assigned the SRC gene to 20q12-q13 by in situ hybridization. Lebo et al. (1984) and Parker et al. (1985) confirmed the assignment by dual-beam chromosome sorting and spot blot DNA analysis. Le Beau et al. (1985) found that deletions of 20q in myeloid disorders were actually interstitial although they appeared to be terminal; thus, the interstitial deletion had resulted in a shift at the SRC locus from 20q313 to the 20q breakpoint region. (FGR OMIM Ref. No. 164940.) Azarnia et al. (1988) found that overexpression of the SRC gene in NIH 3T3 cells caused reduction of cell-to-cell transmission of molecules in the 400- to 700-dalton range. Downregulation was enhanced by point mutation of tyrosine-527,



whereas mutation of tyrosine-416 suppressed both the downregulation of communication by the tyr-527 mutation and that by gene overexpression. The regulation of communication by SRC may be important in the control of embryonic development and cellular growth. By in situ hybridization, Morris et al. (1989) placed the SRC gene at 20q11.2. They observed a secondary peak of grains in the region 20q13.2-qter, the localization of SRC suggested by previous in situ studies. Furthermore, Morris et al. (1989) found that 1 allele of the SRC gene was lost in 2 patients with leukemia and a deletion in 20q. They suggested that the deletions were interstitial. The new assignment, 20q11.2, is consistent with the assignment of HCK (OMIM Ref. No. 142370) which presumably belongs to the same gene family, having originated from a common ancestral gene.

[28880] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28881] Irby, R. B.; Mao, W.; Coppola, D.; Kang, J.; Loubeau, J. M.; Trudeau, W.; Karl, R.; Fujita, D. J.; Jove, R.; Yeatman, T. J. : Activating SRC mutation in a subset of advanced human colon cancers. *Nature Genet.* 21: 187-190, 1999. ; and

[28882] Azarnia, R.; Reddy, S.; Kmiecik, T. E.; Shalloway, D.; Loewenstein, W. R. : The cellular src gene product regulates junctional cell-to-cell communication. Science 239: 398-401, 1988.

[28883] Further studies establishing the function and utilities of SRC are found in John Hopkins OMIM database record ID 190090, and in cited publications numbered 9787-9791, 10883-10884, 9792, 12536, 10801-9796, 355 and 9797 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Suppressor of Fused Homolog (Drosophila) (SUFU, Accession NM\_016169) is another VGAM721 host target gene. SUFU BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SUFU, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SUFU BINDING SITE, designated SEQ ID:18254, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28884] Another function of VGAM721 is therefore inhibition of Suppressor of Fused Homolog (Drosophila) (SUFU, Accession NM\_016169). Accordingly, utilities of VGAM721 in-

clude diagnosis, prevention and treatment of diseases and clinical conditions associated with SUFU. FLJ22596 (Accession NM\_025086) is another VGAM721 host target gene. FLJ22596 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ22596, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22596 BINDING SITE, designated SEQ ID:24704, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28885] Another function of VGAM721 is therefore inhibition of FLJ22596 (Accession NM\_025086). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22596. KIAA0229 (Accession XM\_166478) is another VGAM721 host target gene. KIAA0229 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0229 BINDING SITE,

designated SEQ ID:44402, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28886] Another function of VGAM721 is therefore inhibition of KIAA0229 (Accession XM\_166478). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0229. KIAA1228 (Accession XM\_036408) is another VGAM721 host target gene. KIAA1228 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1228 BINDING SITE, designated SEQ ID:32443, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28887] Another function of VGAM721 is therefore inhibition of KIAA1228 (Accession XM\_036408). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1228. Syntaxin 6 (STX6, Accession NM\_005819) is another VGAM721 host target gene. STX6 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STX6 BINDING SITE, designated SEQ ID:12419, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28888] Another function of VGAM721 is therefore inhibition of Syntaxin 6 (STX6, Accession NM\_005819). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STX6. LOC126661 (Accession XM\_059061) is another VGAM721 host target gene. LOC126661 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC126661, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126661 BINDING SITE, designated SEQ ID:36852, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28889] Another function of VGAM721 is therefore inhibition of

LOC126661 (Accession XM\_059061). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126661. LOC146823 (Accession XM\_097105) is another VGAM721 host target gene. LOC146823 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146823, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146823 BINDING SITE, designated SEQ ID:40749, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28890] Another function of VGAM721 is therefore inhibition of LOC146823 (Accession XM\_097105). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146823. LOC152018 (Accession XM\_098156) is another VGAM721 host target gene. LOC152018 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152018, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC152018 BINDING SITE, designated SEQ ID:41419, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28891] Another function of VGAM721 is therefore inhibition of LOC152018 (Accession XM\_098156). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152018. LOC157278 (Accession XM\_098741) is another VGAM721 host target gene. LOC157278 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157278, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157278 BINDING SITE, designated SEQ ID:41776, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28892] Another function of VGAM721 is therefore inhibition of LOC157278 (Accession XM\_098741). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157278. LOC219855 (Accession XM\_166184) is an-

other VGAM721 host target gene. LOC219855 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219855, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219855 BINDING SITE, designated SEQ ID:43995, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28893] Another function of VGAM721 is therefore inhibition of LOC219855 (Accession XM\_166184). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219855. LOC255461 (Accession XM\_173207) is another VGAM721 host target gene. LOC255461 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255461, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255461 BINDING SITE, designated SEQ ID:46462, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.



[28894] Another function of VGAM721 is therefore inhibition of LOC255461 (Accession XM\_173207). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255461. LOC255516 (Accession XM\_173212) is another VGAM721 host target gene. LOC255516 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255516, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255516 BINDING SITE, designated SEQ ID:46468, to the nucleotide sequence of VGAM721 RNA, herein designated VGAM RNA, also designated SEQ ID:3432.

[28895] Another function of VGAM721 is therefore inhibition of LOC255516 (Accession XM\_173212). Accordingly, utilities of VGAM721 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255516. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 722 (VGAM722) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[28896] VGAM722 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM722 was detected is described hereinabove with reference to Figs. 1–8.

[28897] VGAM722 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Mosaic Virus. VGAM722 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28898] VGAM722 gene encodes a VGAM722 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM722 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM722 precursor RNA is designated SEQ ID:708, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:708 is located at position 1585 relative to the genome of Tomato Mosaic Virus.

[28899] VGAM722 precursor RNA folds onto itself, forming VGAM722 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[28900] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM722 folded precursor RNA into VGAM722 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 41%) nucleotide se-  
quence of VGAM722 RNA is designated SEQ ID:3433, and  
is provided hereinbelow with reference to the sequence  
listing part.

[28901] VGAM722 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM722 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM722 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28902] VGAM722 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM722 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM722 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM722 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM722 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28903] The complementary binding of VGAM722 RNA, herein designated VGAM RNA, to host target binding sites on VGAM722 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM722 host target RNA into VGAM722 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28904] It is appreciated that VGAM722 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM722 host target genes. The mRNA of each one of this plurality of VGAM722 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM722 RNA, herein designated VGAM RNA, and which when bound by VGAM722 RNA causes inhibition of translation of respective one or more VGAM722 host target proteins.

[28905] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM722 gene, herein designated VGAM GENE, on one or more VGAM722 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28906] It is yet further appreciated that a function of VGAM722 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of viral infection by Tomato Mosaic Virus. Specific functions, and accordingly utilities, of VGAM722 correlate with, and may be deduced from, the identity of the host target genes which VGAM722 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

[28907] Nucleotide sequences of the VGAM722 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM722 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM722 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM722 are further described hereinbelow with reference to Table 1.

[28908] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM722 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM722 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28909] As mentioned hereinabove with reference to Fig. 1, a function of VGAM722 gene, herein designated VGAM is inhibition of expression of VGAM722 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM722 correlate with, and may be deduced from, the identity of the target genes which VGAM722 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28910] Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104) is a VGAM722 host target gene. BACE BINDING SITE1 and BACE BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by BACE, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACE BINDING SITE1 and BACE BINDING SITE2, designated SEQ ID:14413 and SEQ ID:29081 respectively, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28911] A function of VGAM722 is therefore inhibition of Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104), a gene which is responsible for the proteolytic processing of the amyloid precursor protein. Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACE. The function of BACE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM173. Carbohydrate (N-acetylglucosamine 6-O) Sulfotransferase 6 (CHST6, Accession NM\_021615) is another



VGAM722 host target gene. CHST6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHST6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST6 BINDING SITE, designated SEQ ID:22243, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28912] Another function of VGAM722 is therefore inhibition of Carbohydrate (N-acetylglucosamine 6-O) Sulfotransferase 6 (CHST6, Accession NM\_021615). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHST6. Formin 2 (FMN2, Accession XM\_086525) is another VGAM722 host target gene. FMN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FMN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FMN2 BINDING SITE, designated SEQ ID:38740, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3433.

[28913] Another function of VGAM722 is therefore inhibition of Formin 2 (FMN2, Accession XM\_086525). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FMN2. Interleukin 20 Receptor, Alpha (IL20RA, Accession NM\_014432) is another VGAM722 host target gene. IL20RA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL20RA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL20RA BINDING SITE, designated SEQ ID:15788, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28914] Another function of VGAM722 is therefore inhibition of Interleukin 20 Receptor, Alpha (IL20RA, Accession NM\_014432), a gene which is the receptor for interleukin-20. Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL20RA. The function of IL20RA and its association with various diseases and clinical condi-

tions, has been established by previous studies, as described hereinabove with reference to VGAM315. Protocadherin Beta 12 (PCDHB12, Accession NM\_018932) is another VGAM722 host target gene. PCDHB12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHB12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHB12 BINDING SITE, designated SEQ ID:21002, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28915] Another function of VGAM722 is therefore inhibition of Protocadherin Beta 12 (PCDHB12, Accession NM\_018932). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHB12. Protocadherin Beta 7 (PCDHB7, Accession NM\_018940) is another VGAM722 host target gene. PCDHB7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHB7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of PCDHB7 BINDING SITE, designated SEQ ID:21007, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28916] Another function of VGAM722 is therefore inhibition of Protocadherin Beta 7 (PCDHB7, Accession NM\_018940). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHB7. FLJ22167 (Accession NM\_024533) is another VGAM722 host target gene. FLJ22167 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22167, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22167 BINDING SITE, designated SEQ ID:23738, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28917] Another function of VGAM722 is therefore inhibition of FLJ22167 (Accession NM\_024533). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ22167. KIAA0737 (Accession NM\_014828) is another VGAM722 host target gene. KIAA0737 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0737, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0737 BINDING SITE, designated SEQ ID:16817, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28918] Another function of VGAM722 is therefore inhibition of KIAA0737 (Accession NM\_014828). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0737. SE70-2 (Accession NM\_022118) is another VGAM722 host target gene. SE70-2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SE70-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SE70-2 BINDING SITE, designated SEQ ID:22662, to the nucleotide se-

quence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28919] Another function of VGAM722 is therefore inhibition of SE70-2 (Accession NM\_022118). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SE70-2. LOC112817 (Accession NM\_138413) is another VGAM722 host target gene. LOC112817 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC112817, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112817 BINDING SITE, designated SEQ ID:28779, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28920] Another function of VGAM722 is therefore inhibition of LOC112817 (Accession NM\_138413). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112817. LOC112840 (Accession NM\_080666) is another VGAM722 host target gene. LOC112840 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC112840, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112840 BINDING SITE, designated SEQ ID:27954, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28921] Another function of VGAM722 is therefore inhibition of LOC112840 (Accession NM\_080666). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112840. LOC158332 (Accession XM\_088554) is another VGAM722 host target gene. LOC158332 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158332, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158332 BINDING SITE, designated SEQ ID:39822, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28922] Another function of VGAM722 is therefore inhibition of LOC158332 (Accession XM\_088554). Accordingly, utilities

of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158332. LOC254549 (Accession XM\_171404) is another VGAM722 host target gene. LOC254549 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254549, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254549 BINDING SITE, designated SEQ ID:46045, to the nucleotide sequence of VGAM722 RNA, herein designated VGAM RNA, also designated SEQ ID:3433.

[28923] Another function of VGAM722 is therefore inhibition of LOC254549 (Accession XM\_171404). Accordingly, utilities of VGAM722 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254549. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 723 (VGAM723) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.



[28924] VGAM723 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM723 was detected is described hereinabove with reference to Figs. 1–8.

[28925] VGAM723 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Mosaic Virus. VGAM723 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28926] VGAM723 gene encodes a VGAM723 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM723 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM723 precursor RNA is designated SEQ ID:709, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:709 is located at position 2545 relative to the genome of Tomato Mosaic Virus.

[28927] VGAM723 precursor RNA folds onto itself, forming VGAM723 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28928] An enzyme complex designated DICER COMPLEX, `dices` the VGAM723 folded precursor RNA into VGAM723 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM723 RNA is designated SEQ ID:3434, and is provided hereinbelow with reference to the sequence listing part.

[28929] VGAM723 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM723 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM723 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[28930] VGAM723 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM723 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM723 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM723 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM723 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28931] The complementary binding of VGAM723 RNA, herein designated VGAM RNA, to host target binding sites on VGAM723 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM723 host target RNA into VGAM723 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28932] It is appreciated that VGAM723 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM723 host target genes. The mRNA of each one of this plurality of VGAM723 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM723 RNA, herein designated VGAM RNA, and which when bound by VGAM723 RNA causes inhibition of translation of respective one or more VGAM723 host target proteins.

[28933] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM723 gene, herein designated VGAM GENE, on one or more VGAM723 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28934] It is yet further appreciated that a function of VGAM723 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of viral infection by Tomato Mosaic Virus. Specific functions, and accordingly utilities, of VGAM723 correlate with, and may be deduced from, the identity of the host target genes which VGAM723 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28935] Nucleotide sequences of the VGAM723 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM723 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM723 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM723 are further  
described hereinbelow with reference to Table 1.

[28936] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM723 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM723 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[28937] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM723 gene, herein designated VGAM is  
inhibition of expression of VGAM723 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM723 correlate with, and may be deduced  
from, the identity of the target genes which VGAM723  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[28938] Aldolase A, Fructose-bisphosphate (ALDOA, Accession  
NM\_000034) is a VGAM723 host target gene. ALDOA

BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ALDOA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALDOA BINDING SITE, designated SEQ ID:5473, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28939] A function of VGAM723 is therefore inhibition of Aldolase A, Fructose-bisphosphate (ALDOA, Accession NM\_000034). Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALDOA. Keratocan (KERA, Accession NM\_007035) is another VGAM723 host target gene. KERA BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KERA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KERA BINDING SITE, designated SEQ ID:13906, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28940] Another function of VGAM723 is therefore inhibition of

Keratocan (KERA, Accession NM\_007035), a gene which may be important in developing and maintaining corneal transparency and for the structure of the stromal matrix. Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KERA. The function of KERA has been established by previous studies. Keratan sulfate proteoglycans (KSPGs) are members of the small leucine-rich proteoglycan (SLRP) family. KSPGs, particularly keratocan, lumican (OMIM Ref. No. 600616), and mimecan (OMIM Ref. No. 602383), are important to the transparency of the cornea. Liu et al. (1998) isolated mouse keratocan cDNA and genomic DNA. Mouse keratocan cDNA predicts a 351-amino acid polypeptide containing a conserved central leucine-rich repeat region. Northern blot analysis of mouse tissues revealed that keratocan is expressed selectively in the eye throughout development. In situ hybridization demonstrated that keratocan is expressed early in neural crest development and later in corneal stromal cells. Tasheva et al. (1999) isolated the cDNA and identified the genomic structure of the human keratocan gene. The gene is spread over 7.65 kb of DNA and contains 3 exons. An open reading frame starting at the be-



gining of the second exon encodes a protein of 352 amino acids. The amino acid sequence of keratocan shows high identity among mammalian species. This evolutionary conservation between the keratocan proteins as well as the restricted expression of the KERA gene in cornea suggests that this molecule might be important in developing and maintaining corneal transparency.

[28941] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28942] Liu, C.-Y.; Shiraishi, A.; Kao, C. W.-C.; Converse, R. L.; Funderburgh, J. L.; Corpuz, L. M.; Conrad, G. W.; Kao, W. W.-Y. : The cloning of mouse keratocan cDNA and genomic DNA and the characterization of its expression during eye development. J. Biol. Chem. 273: 22584-22588, 1998. ; and

[28943] Tasheva, E. S.; Funderburgh, J. L.; Funderburgh, M. L.; Corpuz, L. M.; Conrad, G. W. : Structure and sequence of the gene encoding human keratocan. DNA Seq. 10: 67-74, 1999.

[28944] Further studies establishing the function and utilities of KERA are found in John Hopkins OMIM database record ID 603288, and in cited publications numbered 5339,

10027, 359 and 5341–5342 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phospholipase A2, Group IID (PLA2G2D, Accession NM\_012400) is another VGAM723 host target gene. PLA2G2D BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLA2G2D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLA2G2D BINDING SITE, designated SEQ ID:14775, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28945] Another function of VGAM723 is therefore inhibition of Phospholipase A2, Group IID (PLA2G2D, Accession NM\_012400), a gene which is involved in phospholipid digestion, remodeling of cell membranes, and host defense, as well as pathophysiologic processes. Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLA2G2D. The function of PLA2G2D and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove

with reference to VGAM74.Podocalyxin-like (PODXL, Accession NM\_005397) is another VGAM723 host target gene. PODXL BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PODXL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PODXL BINDING SITE, designated SEQ ID:11870, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28946] Another function of VGAM723 is therefore inhibition of Podocalyxin-like (PODXL, Accession NM\_005397), a gene which is an antiadhesin. Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PODXL. The function of PODXL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247.Adaptor-related Protein Complex 3, Sigma 2 Subunit (AP3S2, Accession NM\_005829) is another VGAM723 host target gene. AP3S2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by AP3S2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP3S2 BINDING SITE, designated SEQ ID:12439, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28947] Another function of VGAM723 is therefore inhibition of Adaptor-related Protein Complex 3, Sigma 2 Subunit (AP3S2, Accession NM\_005829). Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP3S2. Phytanoyl-CoA Hydroxylase Interacting Protein (PHYHIP, Accession NM\_014759) is another VGAM723 host target gene. PHYHIP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PHYHIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PHYHIP BINDING SITE, designated SEQ ID:16509, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28948] Another function of VGAM723 is therefore inhibition of Phytanoyl-CoA Hydroxylase Interacting Protein (PHYHIP, Accession NM\_014759). Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PHYHIP.

LOC136183 (Accession XM\_069753) is another VGAM723 host target gene. LOC136183 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC136183, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC136183 BINDING SITE, designated SEQ ID:37391, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28949] Another function of VGAM723 is therefore inhibition of LOC136183 (Accession XM\_069753). Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC136183. LOC150819 (Accession XM\_097954) is another VGAM723 host target gene. LOC150819 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150819, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150819 BINDING SITE, designated SEQ ID:41245, to the nucleotide sequence of VGAM723 RNA, herein designated VGAM RNA, also designated SEQ ID:3434.

[28950] Another function of VGAM723 is therefore inhibition of LOC150819 (Accession XM\_097954). Accordingly, utilities of VGAM723 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150819. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 724 (VGAM724) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28951] VGAM724 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM724 was detected is described hereinabove with reference to Figs. 1–8.

[28952] VGAM724 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Mosaic Virus.

VGAM724 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28953] VGAM724 gene encodes a VGAM724 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM724 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM724 precursor RNA is designated SEQ ID:710, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:710 is located at position 3312 relative to the genome of Tomato Mosaic Virus.

[28954] VGAM724 precursor RNA folds onto itself, forming VGAM724 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28955] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM724 folded precursor RNA into VGAM724 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM724 RNA is designated SEQ ID:3435, and is provided hereinbelow with reference to the sequence listing part.

[28956] VGAM724 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM724 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM724 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28957] VGAM724 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM724 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-



cleotide sequence of VGAM724 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM724 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM724 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[28958] The complementary binding of VGAM724 RNA, herein designated VGAM RNA, to host target binding sites on VGAM724 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM724 host target RNA into VGAM724 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28959] It is appreciated that VGAM724 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM724 host target genes. The mRNA of each one of this plurality of VGAM724 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM724 RNA, herein designated VGAM RNA, and which when bound by VGAM724 RNA causes inhibition of translation of respective one or more VGAM724 host target proteins.

[28960] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM724 gene, herein designated VGAM GENE, on one or more VGAM724 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28961] It is yet further appreciated that a function of VGAM724 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM724 include diagnosis, prevention and treatment of viral infection by Tomato Mosaic Virus. Specific functions, and accordingly utilities, of VGAM724 correlate with, and may be deduced from, the identity of the host target genes which VGAM724 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28962] Nucleotide sequences of the VGAM724 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM724 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM724 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM724 are further described hereinbelow with reference to Table 1.

[28963] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM724 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM724 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28964] As mentioned hereinabove with reference to Fig. 1, a function of VGAM724 gene, herein designated VGAM is inhibition of expression of VGAM724 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM724 correlate with, and may be deduced from, the identity of the target genes which VGAM724 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28965] Amyloid Beta Precursor Protein (cytoplasmic tail) Binding Protein 2 (APPBP2, Accession NM\_006380) is a VGAM724 host target gene. APPBP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APPBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APPBP2 BINDING SITE, des-

ignated SEQ ID:13078, to the nucleotide sequence of VGAM724 RNA, herein designated VGAM RNA, also designated SEQ ID:3435.

[28966] A function of VGAM724 is therefore inhibition of Amyloid Beta Precursor Protein (cytoplasmic tail) Binding Protein 2 (APPBP2, Accession NM\_006380), a gene which interacts with the basolateral sorting signal of amyloid precursor protein. Accordingly, utilities of VGAM724 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APPBP2. The function of APPBP2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM525.BTB and CNC Homology 1, Basic Leucine Zipper Transcription Factor 1 (BACH1, Accession NM\_001186) is another VGAM724 host target gene. BACH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BACH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACH1 BINDING SITE, designated SEQ ID:6853, to the nucleotide sequence of VGAM724 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3435.

[28967] Another function of VGAM724 is therefore inhibition of BTB and CNC Homology 1, Basic Leucine Zipper Transcription Factor 1 (BACH1, Accession NM\_001186), a gene which acts as repressor or activator, binds to nf-e2 binding sites. Accordingly, utilities of VGAM724 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACH1. The function of BACH1 has been established by previous studies. Members of the small Maf family are basic region leucine zipper (bZip) proteins that can function as transcriptional activators or repressors (see OMIM Ref. No. MAFG, 602020). Small Maf proteins can switch from transcriptional repressors to activators, depending on the proteins with which they form heterodimers. Using a yeast 2 hybrid screen to identify MafK (OMIM Ref. No. 600197) heterodimerization partners, Oyake et al. (1996) identified mouse cDNAs encoding Bach1 and Bach2. Both Bach proteins contained a BTB (broad complex-tramtrack-bric-a-brac) or POZ (poxvirus and zinc finger) protein interaction domain and a CNC (Cap'n'collar)-type bZip domain. Oyake et al. (1996) demonstrated that Bach1 and Bach2 (OMIM Ref. No. 605394) form heterodimers with MafK, and function as

transcriptional activators or repressors when expressed in mammalian cells. Therefore, the authors suggested that the Bach proteins play important roles in coordinating transcription activation and repression by MafK. While developing a physical map of chromosome 21, both Ohira et al. (1998) and Blouin et al. (1998) isolated cDNAs encoding human BACH1. Ohira et al. (1998) reported that the sequence of the predicted 736-amino acid human protein is 80% identical to that of mouse Bach1. Human BACH1, like mouse Bach1, contains a BTB domain and CNC bZip domain. Northern analysis revealed that BACH1 is expressed ubiquitously as a 5.5-kb mRNA. An additional strong 3-kb signal was seen in testis.

[28968] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[28969] Ohira, M.; Seki, N.; Nagase, T.; Ishikawa, K.; Nomura, N.; Ohara, O. : Characterization of a human homolog (BACH1) of the mouse Bach1 gene encoding a BTB-basic leucine zipper transcription factor and its mapping to chromosome 21q22.1. *Genomics* 47: 300-306, 1998. ; and

[28970] Oyake, T.; Itoh, K.; Motohashi 1. Blouin, J.-L.; Sail, G. D.; Guipponi, M.; Rossier, C.; Pappasavas, M.-P.; Antonarakis,

S. E. : Isolation of the human BACH1 transcription regulator gene.

[28971] Further studies establishing the function and utilities of BACH1 are found in John Hopkins OMIM database record ID 602751, and in cited publications numbered 2414, 586 and 5881–5882 listed in the bibliography section herein–below, which are also hereby incorporated by reference. LOC145371 (Accession XM\_085123) is another VGAM724 host target gene. LOC145371 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC145371, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145371 BINDING SITE, designated SEQ ID:37839, to the nucleotide sequence of VGAM724 RNA, herein designated VGAM RNA, also designated SEQ ID:3435.

[28972] Another function of VGAM724 is therefore inhibition of LOC145371 (Accession XM\_085123). Accordingly, utilities of VGAM724 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145371. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the



present invention, referred to here as Viral Genomic Address Messenger 725 (VGAM725) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[28973] VGAM725 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM725 was detected is described hereinabove with reference to Figs. 1–8.

[28974] VGAM725 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Mosaic Virus. VGAM725 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[28975] VGAM725 gene encodes a VGAM725 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM725 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM725 precursor RNA is designated SEQ ID:711, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:711 is located at position 4413 relative to the genome of Tomato

## Mosaic Virus.

[28976] VGAM725 precursor RNA folds onto itself, forming VGAM725 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[28977] An enzyme complex designated DICER COMPLEX, `dices` the VGAM725 folded precursor RNA into VGAM725 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM725 RNA is designated SEQ ID:3436, and is provided hereinbelow with reference to the sequence listing part.

[28978] VGAM725 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM725 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM725 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[28979] VGAM725 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM725 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM725 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM725 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM725 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[28980] The complementary binding of VGAM725 RNA, herein designated VGAM RNA, to host target binding sites on VGAM725 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM725 host target RNA into VGAM725 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[28981] It is appreciated that VGAM725 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM725 host target genes. The mRNA of each one of this plurality of VGAM725 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM725 RNA, herein designated VGAM RNA, and which when bound by VGAM725 RNA causes inhibition of translation of respective one or more VGAM725 host target proteins.

[28982] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM725 gene, herein designated VGAM GENE, on one or more VGAM725 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[28983] It is yet further appreciated that a function of VGAM725 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of viral infection by Tomato Mosaic Virus. Specific functions, and accordingly utilities, of VGAM725 cor-

relate with, and may be deduced from, the identity of the host target genes which VGAM725 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[28984] Nucleotide sequences of the VGAM725 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM725 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM725 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM725 are further described hereinbelow with reference to Table 1.

[28985] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM725 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM725 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[28986] As mentioned hereinabove with reference to Fig. 1, a function of VGAM725 gene, herein designated VGAM is inhibition of expression of VGAM725 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM725 correlate with, and may be deduced

from, the identity of the target genes which VGAM725 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[28987] Amyloid Beta (A4) Precursor Protein-binding, Family A, Member 1 (X11) (APBA1, Accession XM\_046018) is a VGAM725 host target gene. APBA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APBA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APBA1 BINDING SITE, designated SEQ ID:34648, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28988] A function of VGAM725 is therefore inhibition of Amyloid Beta (A4) Precursor Protein-binding, Family A, Member 1 (X11) (APBA1, Accession XM\_046018), a gene which stabilises APP and inhibits production of proteolytic APP fragments. Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APBA1. The function of APBA1 and its association with various diseases and clinical conditions, has been established by previous studies, as de-

scribed hereinabove with reference to VGAM247. Histone Deacetylase 5 (HDAC5, Accession NM\_139205) is another VGAM725 host target gene. HDAC5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HDAC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HDAC5 BINDING SITE, designated SEQ ID:29222, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28989] Another function of VGAM725 is therefore inhibition of Histone Deacetylase 5 (HDAC5, Accession NM\_139205), a gene which is responsible for the deacetylation of lysine residues on the n-terminal part of the core histones and mediate transcriptional regulation. Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HDAC5. The function of HDAC5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM263. Potassium Voltage-gated Channel, Shal-related Subfamily, Member 2 (KCND2, Accession



NM\_012281) is another VGAM725 host target gene. KCND2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCND2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCND2 BINDING SITE, designated SEQ ID:14608, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28990] Another function of VGAM725 is therefore inhibition of Potassium Voltage-gated Channel, Shal-related Subfamily, Member 2 (KCND2, Accession NM\_012281), a gene which is prominent in the repolarization phase of the action potential. Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCND2. The function of KCND2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM449. N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243) is another VGAM725 host target gene. NDRG1 BINDING SITE is HOST TARGET binding site found

in the 3` untranslated region of mRNA encoded by NDRG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDRG1 BINDING SITE, designated SEQ ID:29966, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28991] Another function of VGAM725 is therefore inhibition of N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243), a gene which may have a growth inhibitory role. Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDRG1. The function of NDRG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM144.KIAA1297 (Accession XM\_051005) is another VGAM725 host target gene. KIAA1297 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1297, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1297 BINDING SITE, designated SEQ ID:35710, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28992] Another function of VGAM725 is therefore inhibition of KIAA1297 (Accession XM\_051005). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1297. Opiate Receptor-like 1 (OPRL1, Accession NM\_000913) is another VGAM725 host target gene. OPRL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OPRL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OPRL1 BINDING SITE, designated SEQ ID:6615, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28993] Another function of VGAM725 is therefore inhibition of Opiate Receptor-like 1 (OPRL1, Accession NM\_000913). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OPRL1. Protein Phosphatase 2 (formerly

2A), Regulatory Subunit B", Alpha (PPP2R3A, Accession NM\_002718) is another VGAM725 host target gene. PPP2R3A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PPP2R3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R3A BINDING SITE, designated SEQ ID:8584, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28994] Another function of VGAM725 is therefore inhibition of Protein Phosphatase 2 (formerly 2A), Regulatory Subunit B", Alpha (PPP2R3A, Accession NM\_002718). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R3A. RA-GEF-2 (Accession NM\_016340) is another VGAM725 host target gene. RA-GEF-2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RA-GEF-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RA-

GEF-2 BINDING SITE, designated SEQ ID:18464, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28995] Another function of VGAM725 is therefore inhibition of RA-GEF-2 (Accession NM\_016340). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RA-GEF-2. LOC126961 (Accession XM\_059101) is another VGAM725 host target gene. LOC126961 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC126961, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126961 BINDING SITE, designated SEQ ID:36886, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28996] Another function of VGAM725 is therefore inhibition of LOC126961 (Accession XM\_059101). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126961. LOC201696 (Accession XM\_032269) is another VGAM725 host target gene. LOC201696 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201696 BINDING SITE, designated SEQ ID:31627, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28997] Another function of VGAM725 is therefore inhibition of LOC201696 (Accession XM\_032269). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201696. LOC255042 (Accession XM\_170896) is another VGAM725 host target gene. LOC255042 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255042, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255042 BINDING SITE, designated SEQ ID:45648, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28998] Another function of VGAM725 is therefore inhibition of

LOC255042 (Accession XM\_170896). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255042. LOC257395 (Accession XM\_170919) is another VGAM725 host target gene. LOC257395 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257395, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257395 BINDING SITE, designated SEQ ID:45694, to the nucleotide sequence of VGAM725 RNA, herein designated VGAM RNA, also designated SEQ ID:3436.

[28999] Another function of VGAM725 is therefore inhibition of LOC257395 (Accession XM\_170919). Accordingly, utilities of VGAM725 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257395. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 726 (VGAM726) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[29000] VGAM726 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM726 was detected is described hereinabove with reference to Figs. 1–8.

[29001] VGAM726 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Tomato Mosaic Virus. VGAM726 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29002] VGAM726 gene encodes a VGAM726 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM726 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM726 precursor RNA is designated SEQ ID:712, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:712 is located at position 3315 relative to the genome of Tomato Mosaic Virus.

[29003] VGAM726 precursor RNA folds onto itself, forming VGAM726 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional



`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[29004] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM726 folded precursor RNA into VGAM726 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM726 RNA is designated SEQ ID:3437, and  
is provided hereinbelow with reference to the sequence  
listing part.

[29005] VGAM726 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM726 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM726 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[29006] VGAM726 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM726 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM726 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM726 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM726 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[29007] The complementary binding of VGAM726 RNA, herein designated VGAM RNA, to host target binding sites on VGAM726 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM726 host target RNA into VGAM726 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29008] It is appreciated that VGAM726 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM726 host target genes. The mRNA of each one of this plurality of VGAM726 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM726 RNA, herein designated VGAM RNA, and which when bound by VGAM726 RNA causes inhibition of translation of respective one or more VGAM726 host target proteins.

[29009] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM726 gene, herein designated VGAM GENE, on one or

more VGAM726 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29010] It is yet further appreciated that a function of VGAM726 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of viral infection by Tomato Mosaic Virus. Specific functions, and accordingly utilities, of VGAM726 correlate with, and may be deduced from, the identity of the host target genes which VGAM726 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [29011] Nucleotide sequences of the VGAM726 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM726 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM726 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM726 are further described hereinbelow with reference to Table 1.
- [29012] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM726 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM726 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [29013] As mentioned hereinabove with reference to Fig. 1, a function of VGAM726 gene, herein designated VGAM is inhibition of expression of VGAM726 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM726 correlate with, and may be deduced from, the identity of the target genes which VGAM726 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [29014] BTB and CNC Homology 1, Basic Leucine Zipper Transcrip-

tion Factor 1 (BACH1, Accession NM\_001186) is a VGAM726 host target gene. BACH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BACH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACH1 BINDING SITE, designated SEQ ID:6854, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29015] A function of VGAM726 is therefore inhibition of BTB and CNC Homology 1, Basic Leucine Zipper Transcription Factor 1 (BACH1, Accession NM\_001186), a gene which acts as repressor or activator, binds to nf- $\kappa$ B binding sites. Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACH1. The function of BACH1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM724. Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 4 (SLC4A4, Accession NM\_003759) is another VGAM726 host target gene. SLC4A4 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by SLC4A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC4A4 BINDING SITE, designated SEQ ID:9834, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29016] Another function of VGAM726 is therefore inhibition of Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 4 (SLC4A4, Accession NM\_003759), a gene which is a sodium bicarbonate cotransporter. Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC4A4. The function of SLC4A4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM222.UC28 (Accession NM\_021635) is another VGAM726 host target gene. UC28 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UC28, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of UC28 BINDING SITE, designated SEQ ID:22278, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29017] Another function of VGAM726 is therefore inhibition of UC28 (Accession NM\_021635). Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UC28. FLJ10933 (Accession NM\_018278) is another VGAM726 host target gene. FLJ10933 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10933, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10933 BINDING SITE, designated SEQ ID:20267, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29018] Another function of VGAM726 is therefore inhibition of FLJ10933 (Accession NM\_018278). Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10933. FLJ13659 (Accession NM\_025189) is another VGAM726



host target gene. FLJ13659 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13659, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13659 BINDING SITE, designated SEQ ID:24831, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29019] Another function of VGAM726 is therefore inhibition of FLJ13659 (Accession NM\_025189). Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13659. KIAA1321 (Accession XM\_030856) is another VGAM726 host target gene. KIAA1321 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1321, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1321 BINDING SITE, designated SEQ ID:31191, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29020] Another function of VGAM726 is therefore inhibition of KIAA1321 (Accession XM\_030856). Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1321. LOC145371 (Accession XM\_085123) is another VGAM726 host target gene. LOC145371 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145371, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145371 BINDING SITE, designated SEQ ID:37840, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29021] Another function of VGAM726 is therefore inhibition of LOC145371 (Accession XM\_085123). Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145371. LOC90288 (Accession XM\_030669) is another VGAM726 host target gene. LOC90288 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90288, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90288 BINDING SITE, designated SEQ ID:31103, to the nucleotide sequence of VGAM726 RNA, herein designated VGAM RNA, also designated SEQ ID:3437.

[29022] Another function of VGAM726 is therefore inhibition of LOC90288 (Accession XM\_030669). Accordingly, utilities of VGAM726 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90288. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 727 (VGAM727) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29023] VGAM727 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM727 was detected is described hereinabove with reference to Figs. 1–8.

[29024] VGAM727 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Aconitum Latent Virus. VGAM727 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[29025] VGAM727 gene encodes a VGAM727 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM727 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM727 precursor RNA is designated SEQ ID:713, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:713 is located at position 3494 relative to the genome of Aconitum Latent Virus.

[29026] VGAM727 precursor RNA folds onto itself, forming VGAM727 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29027] An enzyme complex designated DICER COMPLEX, `dices` the VGAM727 folded precursor RNA into VGAM727 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 90%) nucleotide sequence of VGAM727 RNA is designated SEQ ID:3438, and is provided hereinbelow with reference to the sequence listing part.

[29028] VGAM727 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM727 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM727 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29029] VGAM727 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM727 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM727 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM727 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM727 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29030] The complementary binding of VGAM727 RNA, herein designated VGAM RNA, to host target binding sites on VGAM727 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM727 host target RNA into VGAM727 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[29031] It is appreciated that VGAM727 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM727 host target genes. The mRNA of each one of this plurality of VGAM727 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM727 RNA, herein designated VGAM RNA, and which when bound by VGAM727 RNA causes inhibition of translation of respective one or more VGAM727 host target proteins.

[29032] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM727 gene, herein designated VGAM GENE, on one or more VGAM727 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29033] It is yet further appreciated that a function of VGAM727 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of viral infection by Aconitum Latent Virus. Specific functions, and accordingly utilities, of VGAM727 correlate with, and may be deduced from, the identity of the host target genes which VGAM727 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29034] Nucleotide sequences of the VGAM727 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM727 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM727 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM727 are further described hereinbelow with reference to Table 1.

[29035] Nucleotide sequences of host target binding sites, such as



BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM727 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM727 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29036] As mentioned hereinabove with reference to Fig. 1, a function of VGAM727 gene, herein designated VGAM is inhibition of expression of VGAM727 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM727 correlate with, and may be deduced from, the identity of the target genes which VGAM727 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29037] A Disintegrin and Metalloproteinase Domain 19 (meltrin beta) (ADAM19, Accession NM\_033274) is a VGAM727 host target gene. ADAM19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAM19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM19 BINDING SITE, designated SEQ ID:27098, to the nucleotide sequence of

VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29038] A function of VGAM727 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 19 (meltrin beta) (ADAM19, Accession NM\_033274), a gene which participates in the proteolytic processing of beta-type neuregulin isoforms . Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM19. The function of ADAM19 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. Potassium Voltage-gated Channel, Shaker-related Subfamily, Beta Member 1 (KCNAB1, Accession XM\_027634) is another VGAM727 host target gene. KCNAB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNAB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNAB1 BINDING SITE, designated SEQ ID:30547, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ

ID:3438.

[29039] Another function of VGAM727 is therefore inhibition of Potassium Voltage-gated Channel, Shaker-related Subfamily, Beta Member 1 (KCNAB1, Accession XM\_027634), a gene which is the regulatory beta subunit for a shaker-related voltage-gated potassium channel. Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNAB1. The function of KCNAB1 has been established by previous studies. 'Shaker' and other voltage-dependent potassium channel proteins help to determine the electrical properties of excitable cells and play additional physiologic roles in nonexcitable cell types. Voltage-activated, outwardly rectifying potassium channels (Kv) are heterooligomers that are assembled from alpha and beta subunits in a 1:1 molar ratio. Schultz et al. (1996) noted that mammals contain a large number of alpha-subunit potassium channel genes, often clustered within the genome, that may have arisen through local and chromosomal duplication events. The associated beta subunits modulate the gating properties and amplitudes of the Shaker potassium currents. England et al. (1995) cloned a human heart cDNA encoding a beta subunit that

they designated Kv-beta-1.3. Sequence analysis revealed that Kv-beta-1.3 and the previously identified human Kv-beta-1 (England et al., 1995) and Kv-beta-3 (McCormack et al., 1995) subunits differ only at their N termini and are encoded by alternatively spliced mRNAs from a single gene. The authors suggested that Kv-beta-1 and Kv-beta-3 be renamed Kv-beta-1.1 and Kv-beta-1.2, respectively. The predicted 419-amino acid Kv-beta-1.3 subunit does not contain a hydrophobic domain and is likely to be a cytoplasmic protein, like other beta subunits. When coexpressed in *Xenopus* oocytes, the Kv-beta-1.3 subunit altered the functional properties of Kv1.5 (KCNA5; 176267), converting it from a delayed rectifier to a channel with rapid but partial inactivation. In addition, Kv-beta-1.3 converted the Kv1.5 outwardly rectifying current-voltage relationship to one showing strong inward rectification. England et al. (1995) concluded that Kv channel current diversity may arise from association with alternatively spliced Kv-beta subunits. By Northern blot analysis, Leicher et al. (1996) found that the KCNA1B gene was expressed as 3.4- and 3.8-kb mRNAs in human brain. The pattern of expression of Kv1-alpha and Kv-beta subunits suggested an intricate and cell-specific reg-

ulatory mechanism that produces distinct combinations of alpha and beta subunits in different nuclei of the brain.

The Kv-beta-1.1 and Kv-beta-1.2 splice variants contain an N-terminal inactivating domain similar to that found in A-type Kv channels (see OMIM Ref. No. KCNA4; 176266).

When coexpressed in mammalian cells, Kv-beta-1.1 and Kv-beta-1.2 conferred rapid inactivation on Kv1.5 channels, with different potencies

[29040] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29041] Leicher, T. Roeper, J.; Weber, K.; Wang, X.; Pongs, O. : Structural and functional characterization of human potassium channel subunit beta-1 (KCNA1B). *Neuropharmacology* 35: 787-795, 1996. ; and

[29042] Schultz, D.; Litt, M.; Smith, L.; Thayer, M.; McCormack, K. : Localization of two potassium channel beta subunit genes, KCNA1B and KCNA2B. *Genomics* 31: 389-391, 1996.

[29043] Further studies establishing the function and utilities of KCNAB1 are found in John Hopkins OMIM database record ID 601141, and in cited publications numbered 6841-2849 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Polycystic

Kidney Disease (polycystin) and REJ (sperm receptor for egg jelly homolog, sea urchin)-like (PKDREJ, Accession NM\_006071) is another VGAM727 host target gene.

PKDREJ BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PKDREJ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PKDREJ BINDING SITE, designated SEQ ID:12715, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29044] Another function of VGAM727 is therefore inhibition of Polycystic Kidney Disease (polycystin) and REJ (sperm receptor for egg jelly homolog, sea urchin)-like (PKDREJ, Accession NM\_006071), a gene which may intervene in fertilization. Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PKDREJ. The function of PKDREJ and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM641. RAD54B (Accession NM\_134434) is another VGAM727 host target

gene. RAD54B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAD54B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAD54B BINDING SITE, designated SEQ ID:28676, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29045] Another function of VGAM727 is therefore inhibition of RAD54B (Accession NM\_134434), a gene which is involved in dna repair and mitotic recombination. Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAD54B. The function of RAD54B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM595. Sorting Nexin 10 (SNX10, Accession NM\_013322) is another VGAM727 host target gene. SNX10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SNX10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2

illustrates the complementarity of the nucleotide sequences of SNX10 BINDING SITE, designated SEQ ID:14967, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29046] Another function of VGAM727 is therefore inhibition of Sorting Nexin 10 (SNX10, Accession NM\_013322). Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNX10. LOC115294 (Accession XM\_054302) is another VGAM727 host target gene. LOC115294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115294 BINDING SITE, designated SEQ ID:36148, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29047] Another function of VGAM727 is therefore inhibition of LOC115294 (Accession XM\_054302). Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC115294. LOC148254 (Accession XM\_086121) is another VGAM727 host target gene. LOC148254 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148254, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148254 BINDING SITE, designated SEQ ID:38503, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29048] Another function of VGAM727 is therefore inhibition of LOC148254 (Accession XM\_086121). Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148254. LOC164714 (Accession XM\_104657) is another VGAM727 host target gene. LOC164714 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC164714, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164714 BINDING SITE, designated SEQ ID:42181, to the nucleotide sequence of VGAM727 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3438.

[29049] Another function of VGAM727 is therefore inhibition of LOC164714 (Accession XM\_104657). Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC164714. LOC166424 (Accession XM\_105867) is another VGAM727 host target gene. LOC166424 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC166424, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC166424 BINDING SITE, designated SEQ ID:42195, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29050] Another function of VGAM727 is therefore inhibition of LOC166424 (Accession XM\_105867). Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC166424. LOC255096 (Accession XM\_174913) is another VGAM727 host target gene. LOC255096 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255096, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255096 BINDING SITE, designated SEQ ID:46608, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29051] Another function of VGAM727 is therefore inhibition of LOC255096 (Accession XM\_174913). Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255096. LOC91380 (Accession XM\_038134) is another VGAM727 host target gene. LOC91380 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91380, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91380 BINDING SITE, designated SEQ ID:32756, to the nucleotide sequence of VGAM727 RNA, herein designated VGAM RNA, also designated SEQ ID:3438.

[29052] Another function of VGAM727 is therefore inhibition of LOC91380 (Accession XM\_038134). Accordingly, utilities of VGAM727 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC91380. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 728 (VGAM728) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29053] VGAM728 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM728 was detected is described hereinabove with reference to Figs. 1–8.

[29054] VGAM728 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Aconitum Latent Virus. VGAM728 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29055] VGAM728 gene encodes a VGAM728 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM728 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM728 precursor RNA is designated SEQ

ID:714, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:714 is located at position 3248 relative to the genome of Aconitum Latent Virus.

[29056] VGAM728 precursor RNA folds onto itself, forming VGAM728 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29057] An enzyme complex designated DICER COMPLEX, `dices` the VGAM728 folded precursor RNA into VGAM728 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM728 RNA is designated SEQ ID:3439, and is provided hereinbelow with reference to the sequence

listing part.

[29058] VGAM728 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM728 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM728 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29059] VGAM728 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM728 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM728 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM728 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM728 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29060] The complementary binding of VGAM728 RNA, herein designated VGAM RNA, to host target binding sites on VGAM728 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM728 host target RNA into VGAM728 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29061] It is appreciated that VGAM728 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM728 host target genes. The mRNA of each one of this plurality of VGAM728 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM728 RNA, herein designated VGAM

RNA, and which when bound by VGAM728 RNA causes inhibition of translation of respective one or more VGAM728 host target proteins.

[29062] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM728 gene, herein designated VGAM GENE, on one or more VGAM728 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29063] It is yet further appreciated that a function of VGAM728 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,



utilities of VGAM728 include diagnosis, prevention and treatment of viral infection by Aconitum Latent Virus. Specific functions, and accordingly utilities, of VGAM728 correlate with, and may be deduced from, the identity of the host target genes which VGAM728 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29064] Nucleotide sequences of the VGAM728 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM728 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM728 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM728 are further described hereinbelow with reference to Table 1.

[29065] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM728 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM728 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29066] As mentioned hereinabove with reference to Fig. 1, a function of VGAM728 gene, herein designated VGAM is

inhibition of expression of VGAM728 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM728 correlate with, and may be deduced from, the identity of the target genes which VGAM728 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29067] B-cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898) is a VGAM728 host target gene. BCL11B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL11B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL11B BINDING SITE, designated SEQ ID:23159, to the nucleotide sequence of VGAM728 RNA, herein designated VGAM RNA, also designated SEQ ID:3439.

[29068] A function of VGAM728 is therefore inhibition of B-cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898). Accordingly, utilities of VGAM728 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL11B. Chromosome 20 Open Reading Frame 64 (C20orf64, Accession

NM\_033550) is another VGAM728 host target gene. C20orf64 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by C20orf64, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf64 BINDING SITE, designated SEQ ID:27310, to the nucleotide sequence of VGAM728 RNA, herein designated VGAM RNA, also designated SEQ ID:3439.

[29069] Another function of VGAM728 is therefore inhibition of Chromosome 20 Open Reading Frame 64 (C20orf64, Accession NM\_033550). Accordingly, utilities of VGAM728 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf64. KIAA1958 (Accession XM\_088566) is another VGAM728 host target gene. KIAA1958 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1958, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1958 BINDING SITE, designated SEQ ID:39827, to the nucleotide sequence of

VGAM728 RNA, herein designated VGAM RNA, also designated SEQ ID:3439.

[29070] Another function of VGAM728 is therefore inhibition of KIAA1958 (Accession XM\_088566). Accordingly, utilities of VGAM728 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1958. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 729 (VGAM729) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29071] VGAM729 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM729 was detected is described hereinabove with reference to Figs. 1–8.

[29072] VGAM729 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cydia Pomonella Granulovirus. VGAM729 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29073] VGAM729 gene encodes a VGAM729 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM729 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM729 precursor RNA is designated SEQ ID:715, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:715 is located at position 72517 relative to the genome of Cydia Pomonella Granulovirus.

[29074] VGAM729 precursor RNA folds onto itself, forming VGAM729 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29075] An enzyme complex designated DICER COMPLEX, `dices` the VGAM729 folded precursor RNA into VGAM729 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM729 RNA is designated SEQ ID:3440, and is provided hereinbelow with reference to the sequence listing part.

[29076] VGAM729 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM729 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM729 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[29077] VGAM729 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM729 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM729 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM729 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM729 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29078] The complementary binding of VGAM729 RNA, herein designated VGAM RNA, to host target binding sites on VGAM729 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM729 host target RNA into VGAM729 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29079] It is appreciated that VGAM729 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM729 host target genes. The mRNA of each one of this plurality of VGAM729 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM729 RNA, herein designated VGAM RNA, and which when bound by VGAM729 RNA causes inhibition of translation of respective one or more VGAM729 host target proteins.

[29080] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM729 gene, herein designated VGAM GENE, on one or more VGAM729 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,



`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[29081] It is yet further appreciated that a function of VGAM729 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM729 include diagnosis, prevention and treatment of viral infection by Cydia Pomonella Granulovirus. Specific functions, and accordingly utilities, of VGAM729 correlate with, and may be deduced from, the identity of the host target genes which VGAM729 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29082] Nucleotide sequences of the VGAM729 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM729 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM729 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM729 are further described hereinbelow with reference to Table 1.

[29083] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM729 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM729 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29084] As mentioned hereinabove with reference to Fig. 1, a function of VGAM729 gene, herein designated VGAM is inhibition of expression of VGAM729 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM729 correlate with, and may be deduced from, the identity of the target genes which VGAM729 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29085] FLJ10716 (Accession NM\_018191) is a VGAM729 host target gene. FLJ10716 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10716, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10716 BINDING SITE, designated SEQ ID:20046, to the nucleotide sequence of VGAM729 RNA, herein designated VGAM RNA, also designated SEQ ID:3440.

[29086] A function of VGAM729 is therefore inhibition of FLJ10716 (Accession NM\_018191). Accordingly, utilities of

VGAM729 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10716. NTT73 (Accession NM\_018057) is another VGAM729 host target gene. NTT73 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NTT73, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NTT73 BINDING SITE, designated SEQ ID:19822, to the nucleotide sequence of VGAM729 RNA, herein designated VGAM RNA, also designated SEQ ID:3440.

[29087] Another function of VGAM729 is therefore inhibition of NTT73 (Accession NM\_018057). Accordingly, utilities of VGAM729 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NTT73. LOC157562 (Accession XM\_098779) is another VGAM729 host target gene. LOC157562 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC157562, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157562 BINDING

SITE, designated SEQ ID:41818, to the nucleotide sequence of VGAM729 RNA, herein designated VGAM RNA, also designated SEQ ID:3440.

[29088] Another function of VGAM729 is therefore inhibition of LOC157562 (Accession XM\_098779). Accordingly, utilities of VGAM729 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157562. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 730 (VGAM730) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29089] VGAM730 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM730 was detected is described hereinabove with reference to Figs. 1–8.

[29090] VGAM730 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cydia Pomonella Granulovirus. VGAM730 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29091] VGAM730 gene encodes a VGAM730 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM730 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM730 precursor RNA is designated SEQ ID:716, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:716 is located at position 72933 relative to the genome of Cydia Pomonella Granulovirus.

[29092] VGAM730 precursor RNA folds onto itself, forming VGAM730 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29093] An enzyme complex designated DICER COMPLEX, `dices` the VGAM730 folded precursor RNA into VGAM730 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM730 RNA is designated SEQ ID:3441, and is provided hereinbelow with reference to the sequence listing part.

[29094] VGAM730 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM730 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM730 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29095] VGAM730 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM730 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM730 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM730 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM730 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[29096] The complementary binding of VGAM730 RNA, herein designated VGAM RNA, to host target binding sites on VGAM730 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM730 host target RNA into VGAM730 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29097] It is appreciated that VGAM730 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM730 host target genes. The mRNA of each one of this plurality of VGAM730 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM730 RNA, herein designated VGAM RNA, and which when bound by VGAM730 RNA causes inhibition of translation of respective one or more VGAM730 host target proteins.

[29098] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM730 gene, herein designated VGAM GENE, on one or more VGAM730 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these



other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[29099] It is yet further appreciated that a function of VGAM730 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of viral infection by Cydia Pomonella Granulovirus. Specific functions, and accordingly utilities, of VGAM730 correlate with, and may be deduced from, the identity of the host target genes which VGAM730 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29100] Nucleotide sequences of the VGAM730 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM730 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM730 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM730 are further described hereinbelow with reference to Table 1.

[29101] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM730 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM730 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29102] As mentioned hereinabove with reference to Fig. 1, a function of VGAM730 gene, herein designated VGAM is inhibition of expression of VGAM730 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM730 correlate with, and may be deduced from, the identity of the target genes which VGAM730 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29103] ATP-binding Cassette, Sub-family D (ALD), Member 1 (ABCD1, Accession NM\_000033) is a VGAM730 host target gene. ABCD1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ABCD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCD1 BINDING SITE, designated SEQ ID:5470, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29104] A function of VGAM730 is therefore inhibition of ATP-binding Cassette, Sub-family D (ALD), Member 1 (ABCD1, Accession NM\_000033). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCD1. Chromosome 14 Open Reading Frame 1 (C14orf1, Accession NM\_007176) is another VGAM730 host target gene. C14orf1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C14orf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C14orf1 BINDING SITE, designated SEQ ID:14027, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29105] Another function of VGAM730 is therefore inhibition of Chromosome 14 Open Reading Frame 1 (C14orf1, Accession NM\_007176). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C14orf1. Dead Ringer-like 1 (Drosophila) (DRIL1, Accession NM\_005224) is another VGAM730 host target gene. DRIL1 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DRIL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRIL1 BINDING SITE, designated SEQ ID:11718, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29106] Another function of VGAM730 is therefore inhibition of Dead Ringer-like 1 (Drosophila) (DRIL1, Accession NM\_005224), a gene which binds a  $\mu$  promoter proximal site necessary for induced  $\mu$ -heavy-chain transcription. Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRIL1. The function of DRIL1 has been established by previous studies. Herrscher et al. (1995) identified the mouse Bright (B-cell regulator of IgH transcription) gene. They found that the Bright protein is expressed specifically in B cells and transactivates an IgH enhancer in transient transfection assays. Bright and the Drosophila 'dead ringer' (dri) gene product belong to a protein family whose members share a conserved DNA-binding domain termed the 'A/T-rich interaction domain'

(ARID). By PCR using degenerate primers based on the ARID sequence, Kortschak et al. (1998) isolated a HeLa cell cDNA encoding DRIL1. Overall, the predicted protein is 79% identical to mouse Bright. The DNA-binding domain of DRIL1 is highly conserved, sharing 97% and 79% identity with the DNA-binding domain of Bright and DRI, respectively. Northern and dot blot analyses revealed that DRIL1 was expressed as a 4.4-kb mRNA in all tissues tested. The DRIL1 gene contains 8 exons. Kortschak et al. (1998) mapped the DRIL1 gene to 19p13.3 by fluorescence in situ hybridization and by analysis of cosmids from this region.

[29107] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29108] Herrscher, R. F.; Kaplan, M. H.; Lelsz, D. L.; Das, C.; Scheuermann, R.; Tucker, P. W. : The immunoglobulin heavy-chain matrix-associating regions are bound by Bright: a B cell-specific trans-activator that describes a new DNA-binding protein family. *Genes Dev.* 9: 3067-3082, 1995. ; and

[29109] Kortschak, R. D.; Reimann, H.; Zimmer, M.; Eyre, H. J.; Saint, R.; Jenne, D. E. : The human dead ringer/bright ho-

molog, DRIL1: cDNA cloning, gene structure, and mapping to D19S886, a ma.

[29110] Further studies establishing the function and utilities of DRIL1 are found in John Hopkins OMIM database record ID 603265, and in cited publications numbered 6329–6330 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Isoprenylcysteine Carboxyl Methyltransferase (ICMT, Accession NM\_012405) is another VGAM730 host target gene. ICMT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ICMT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ICMT BINDING SITE, designated SEQ ID:14780, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29111] Another function of VGAM730 is therefore inhibition of Isoprenylcysteine Carboxyl Methyltransferase (ICMT, Accession NM\_012405). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ICMT. Ubiquitin-conjugating Enzyme E2L 3 (UBE2L3, Accession

NM\_003347) is another VGAM730 host target gene. UBE2L3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by UBE2L3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2L3 BINDING SITE, designated SEQ ID:9356, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29112] Another function of VGAM730 is therefore inhibition of Ubiquitin-conjugating Enzyme E2L 3 (UBE2L3, Accession NM\_003347), a gene which catalyzes the covalent attachment of ubiquitin to other proteins. Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2L3. The function of UBE2L3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM215.KIAA0329 (Accession NM\_014844) is another VGAM730 host target gene. KIAA0329 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0329, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0329 BINDING SITE, designated SEQ ID:16872, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29113] Another function of VGAM730 is therefore inhibition of KIAA0329 (Accession NM\_014844). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0329. KIAA1554 (Accession XM\_170834) is another VGAM730 host target gene. KIAA1554 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1554, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1554 BINDING SITE, designated SEQ ID:45607, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29114] Another function of VGAM730 is therefore inhibition of KIAA1554 (Accession XM\_170834). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with KIAA1554. PR Domain Containing 7 (PRDM7, Accession NM\_052996) is another VGAM730 host target gene. PRDM7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PRDM7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRDM7 BINDING SITE, designated SEQ ID:27566, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29115] Another function of VGAM730 is therefore inhibition of PR Domain Containing 7 (PRDM7, Accession NM\_052996). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRDM7. PR Domain Containing 9 (PRDM9, Accession NM\_020227) is another VGAM730 host target gene. PRDM9 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PRDM9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of PRDM9 BINDING SITE, designated SEQ ID:21493, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29116] Another function of VGAM730 is therefore inhibition of PR Domain Containing 9 (PRDM9, Accession NM\_020227). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRDM9. RAB40C, Member RAS Oncogene Family (RAB40C, Accession NM\_021168) is another VGAM730 host target gene. RAB40C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB40C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB40C BINDING SITE, designated SEQ ID:22144, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29117] Another function of VGAM730 is therefore inhibition of RAB40C, Member RAS Oncogene Family (RAB40C, Accession NM\_021168). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with RAB40C. SEC8 (Accession NM\_021807) is another VGAM730 host target gene. SEC8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEC8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC8 BINDING SITE, designated SEQ ID:22359, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29118] Another function of VGAM730 is therefore inhibition of SEC8 (Accession NM\_021807). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEC8. Transmembrane Protease, Serine 5 (spinesin) (TMPRSS5, Accession NM\_030770) is another VGAM730 host target gene. TMPRSS5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMPRSS5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMPRSS5 BINDING SITE, designated SEQ ID:25054, to the nucleotide sequence of VGAM730 RNA,

herein designated VGAM RNA, also designated SEQ ID:3441.

[29119] Another function of VGAM730 is therefore inhibition of Transmembrane Protease, Serine 5 (spinesin) (TMPRSS5, Accession NM\_030770). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMPRSS5.

LOC149319 (Accession XM\_086495) is another VGAM730 host target gene. LOC149319 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149319, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149319 BINDING SITE, designated SEQ ID:38712, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29120] Another function of VGAM730 is therefore inhibition of LOC149319 (Accession XM\_086495). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149319. LOC254423 (Accession XM\_173286) is another VGAM730 host target gene. LOC254423 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC254423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254423 BINDING SITE, designated SEQ ID:46528, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29121] Another function of VGAM730 is therefore inhibition of LOC254423 (Accession XM\_173286). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254423. LOC89919 (Accession XM\_027244) is another VGAM730 host target gene. LOC89919 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC89919, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC89919 BINDING SITE, designated SEQ ID:30461, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29122] Another function of VGAM730 is therefore inhibition of

LOC89919 (Accession XM\_027244). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC89919. LOC91812 (Accession XM\_040857) is another VGAM730 host target gene. LOC91812 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC91812, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91812 BINDING SITE, designated SEQ ID:33389, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29123] Another function of VGAM730 is therefore inhibition of LOC91812 (Accession XM\_040857). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91812. LOC91813 (Accession XM\_040862) is another VGAM730 host target gene. LOC91813 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC91813, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of LOC91813 BINDING SITE, designated SEQ ID:33393, to the nucleotide sequence of VGAM730 RNA, herein designated VGAM RNA, also designated SEQ ID:3441.

[29124] Another function of VGAM730 is therefore inhibition of LOC91813 (Accession XM\_040862). Accordingly, utilities of VGAM730 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91813. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 731 (VGAM731) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29125] VGAM731 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM731 was detected is described hereinabove with reference to Figs. 1–8.

[29126] VGAM731 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cydia Pomonella Granulovirus. VGAM731 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in

the human genome.

[29127] VGAM731 gene encodes a VGAM731 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM731 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM731 precursor RNA is designated SEQ ID:717, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:717 is located at position 71312 relative to the genome of Cydia Pomonella Granulovirus.

[29128] VGAM731 precursor RNA folds onto itself, forming VGAM731 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29129] An enzyme complex designated DICER COMPLEX, `dices` the VGAM731 folded precursor RNA into VGAM731 RNA, herein designated VGAM RNA, a single stranded ~22 nt



long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM731 RNA is designated SEQ ID:3442, and is provided hereinbelow with reference to the sequence listing part.

[29130] VGAM731 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM731 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM731 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29131] VGAM731 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM731 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM731 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM731 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM731 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29132] The complementary binding of VGAM731 RNA, herein designated VGAM RNA, to host target binding sites on VGAM731 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM731 host target RNA into VGAM731 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29133] It is appreciated that VGAM731 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM731 host target genes. The mRNA of each one of this plurality of VGAM731 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM731 RNA, herein designated VGAM RNA, and which when bound by VGAM731 RNA causes inhibition of translation of respective one or more VGAM731 host target proteins.

[29134] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM731 gene, herein designated VGAM GENE, on one or more VGAM731 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29135] It is yet further appreciated that a function of VGAM731 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment of viral infection by Cydia Pomonella Granulovirus. Specific functions, and accordingly utilities, of VGAM731 correlate with, and may be deduced from, the identity of the host target genes which VGAM731 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29136] Nucleotide sequences of the VGAM731 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM731 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM731 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM731 are further described hereinbelow with reference to Table 1.

[29137] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM731 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM731 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29138] As mentioned hereinabove with reference to Fig. 1, a function of VGAM731 gene, herein designated VGAM is inhibition of expression of VGAM731 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM731 correlate with, and may be deduced from, the identity of the target genes which VGAM731 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29139] Component of Oligomeric Golgi Complex 7 (COG7, Accession XM\_041725) is a VGAM731 host target gene. COG7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COG7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COG7 BINDING SITE, designated SEQ ID:33577, to the nucleotide sequence of VGAM731 RNA, herein designated VGAM RNA, also designated SEQ ID:3442.

[29140] A function of VGAM731 is therefore inhibition of Component of Oligomeric Golgi Complex 7 (COG7, Accession XM\_041725). Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COG7. FLJ13710 (Accession NM\_024817) is another VGAM731 host target gene. FLJ13710 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13710, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13710 BINDING SITE, designated SEQ ID:24208, to the nucleotide sequence of VGAM731 RNA, herein designated VGAM RNA, also designated SEQ ID:3442.

[29141] Another function of VGAM731 is therefore inhibition of FLJ13710 (Accession NM\_024817). Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13710. KIAA1486 (Accession XM\_041126) is another VGAM731 host target gene. KIAA1486 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1486, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1486 BINDING SITE, designated SEQ ID:33461, to the nucleotide sequence of VGAM731 RNA, herein designated VGAM RNA, also designated SEQ ID:3442.

[29142] Another function of VGAM731 is therefore inhibition of KIAA1486 (Accession XM\_041126). Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1486. KIAA1954 (Accession XM\_085375) is another VGAM731 host target gene. KIAA1954 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1954, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1954 BINDING SITE, designated SEQ ID:38095, to the nucleotide sequence of VGAM731 RNA, herein designated VGAM RNA, also designated SEQ ID:3442.

[29143] Another function of VGAM731 is therefore inhibition of KIAA1954 (Accession XM\_085375). Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1954. MGC2541 (Accession NM\_080670) is another VGAM731 host target gene. MGC2541 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2541, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2541 BINDING SITE, designated SEQ ID:27962, to the nucleotide sequence of VGAM731 RNA, herein designated VGAM RNA, also designated SEQ ID:3442.

[29144] Another function of VGAM731 is therefore inhibition of MGC2541 (Accession NM\_080670). Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2541. Septin 3 (SEPT3, Accession NM\_019106) is another VGAM731 host target gene. SEPT3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEPT3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEPT3 BINDING SITE, designated SEQ ID:21180, to the nucleotide se-



quence of VGAM731 RNA, herein designated VGAM RNA, also designated SEQ ID:3442.

[29145] Another function of VGAM731 is therefore inhibition of Septin 3 (SEPT3, Accession NM\_019106). Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEPT3. LOC146958 (Accession XM\_097142) is another VGAM731 host target gene. LOC146958 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146958, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146958 BINDING SITE, designated SEQ ID:40775, to the nucleotide sequence of VGAM731 RNA, herein designated VGAM RNA, also designated SEQ ID:3442.

[29146] Another function of VGAM731 is therefore inhibition of LOC146958 (Accession XM\_097142). Accordingly, utilities of VGAM731 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146958. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 732 (VGAM732) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29147] VGAM732 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM732 was detected is described hereinabove with reference to Figs. 1–8.

[29148] VGAM732 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cydia Pomonella Granulovirus. VGAM732 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29149] VGAM732 gene encodes a VGAM732 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM732 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM732 precursor RNA is designated SEQ ID:718, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:718 is located at position 73500 relative to the genome of Cydia Pomonella Granulovirus.

[29150] VGAM732 precursor RNA folds onto itself, forming VGAM732 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29151] An enzyme complex designated DICER COMPLEX, `dices` the VGAM732 folded precursor RNA into VGAM732 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM732 RNA is designated SEQ ID:3443, and is provided hereinbelow with reference to the sequence listing part.

[29152] VGAM732 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM732 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM732 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29153] VGAM732 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM732 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM732 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM732 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM732 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29154] The complementary binding of VGAM732 RNA, herein designated VGAM RNA, to host target binding sites on VGAM732 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM732 host target RNA into VGAM732 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29155] It is appreciated that VGAM732 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM732 host target genes. The mRNA of each one of this plurality of VGAM732 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM732 RNA, herein designated VGAM RNA, and which when bound by VGAM732 RNA causes inhibition of translation of respective one or more VGAM732 host target proteins.

[29156] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM732 gene, herein designated VGAM GENE, on one or more VGAM732 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29157] It is yet further appreciated that a function of VGAM732 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM732 include diagnosis, prevention and treatment of viral infection by Cydia Pomonella Granulovirus. Specific functions, and accordingly utilities, of VGAM732 correlate with, and may be deduced from, the

identity of the host target genes which VGAM732 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29158] Nucleotide sequences of the VGAM732 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM732 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM732 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM732 are further described hereinbelow with reference to Table 1.

[29159] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM732 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM732 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29160] As mentioned hereinabove with reference to Fig. 1, a function of VGAM732 gene, herein designated VGAM is inhibition of expression of VGAM732 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM732 correlate with, and may be deduced from, the identity of the target genes which VGAM732

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29161] RP42 (Accession NM\_020640) is a VGAM732 host target gene. RP42 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RP42, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RP42 BINDING SITE, designated SEQ ID:21800, to the nucleotide sequence of VGAM732 RNA, herein designated VGAM RNA, also designated SEQ ID:3443.

[29162] A function of VGAM732 is therefore inhibition of RP42 (Accession NM\_020640), a gene which not clear yet. Accordingly, utilities of VGAM732 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RP42. The function of RP42 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM47. Retinoschisis (X-linked, juvenile) 1 (RS1, Accession NM\_000330) is another VGAM732 host target gene. RS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RS1, corresponding to a



HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RS1 BINDING SITE, designated SEQ ID:5876, to the nucleotide sequence of VGAM732 RNA, herein designated VGAM RNA, also designated SEQ ID:3443.

[29163] Another function of VGAM732 is therefore inhibition of Retinoschisis (X-linked, juvenile) 1 (RS1, Accession NM\_000330). Accordingly, utilities of VGAM732 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RS1. FLJ22940 (Accession NM\_024571) is another VGAM732 host target gene. FLJ22940 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ22940, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22940 BINDING SITE, designated SEQ ID:23797, to the nucleotide sequence of VGAM732 RNA, herein designated VGAM RNA, also designated SEQ ID:3443.

[29164] Another function of VGAM732 is therefore inhibition of FLJ22940 (Accession NM\_024571). Accordingly, utilities of

VGAM732 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22940. Mal, T-cell Differentiation Protein 2 (MAL2, Accession NM\_052886) is another VGAM732 host target gene. MAL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAL2 BINDING SITE, designated SEQ ID:27468, to the nucleotide sequence of VGAM732 RNA, herein designated VGAM RNA, also designated SEQ ID:3443.

[29165] Another function of VGAM732 is therefore inhibition of Mal, T-cell Differentiation Protein 2 (MAL2, Accession NM\_052886). Accordingly, utilities of VGAM732 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAL2. TU3A (Accession NM\_007177) is another VGAM732 host target gene. TU3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TU3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

TU3A BINDING SITE, designated SEQ ID:14032, to the nucleotide sequence of VGAM732 RNA, herein designated VGAM RNA, also designated SEQ ID:3443.

[29166] Another function of VGAM732 is therefore inhibition of TU3A (Accession NM\_007177). Accordingly, utilities of VGAM732 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TU3A. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 733 (VGAM733) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29167] VGAM733 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM733 was detected is described hereinabove with reference to Figs. 1–8.

[29168] VGAM733 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Barley Yellow Mosaic Virus. VGAM733 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29169] VGAM733 gene encodes a VGAM733 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM733 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM733 precursor RNA is designated SEQ ID:719, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:719 is located at position 6830 relative to the genome of Barley Yellow Mosaic Virus.

[29170] VGAM733 precursor RNA folds onto itself, forming VGAM733 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29171] An enzyme complex designated DICER COMPLEX, `dices` the VGAM733 folded precursor RNA into VGAM733 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 78%) nucleotide sequence of VGAM733 RNA is designated SEQ ID:3444, and is provided hereinbelow with reference to the sequence listing part.

[29172] VGAM733 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM733 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM733 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29173] VGAM733 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM733 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM733 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM733 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM733 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29174] The complementary binding of VGAM733 RNA, herein designated VGAM RNA, to host target binding sites on VGAM733 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM733 host target RNA into VGAM733 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29175] It is appreciated that VGAM733 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM733 host target genes. The mRNA of each one of this plurality of VGAM733 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM733 RNA, herein designated VGAM RNA, and which when bound by VGAM733 RNA causes inhibition of translation of respective one or more VGAM733 host target proteins.

[29176] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM733 gene, herein designated VGAM GENE, on one or more VGAM733 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[29177] It is yet further appreciated that a function of VGAM733 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM733 include diagnosis, prevention and treatment of viral infection by Barley Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM733 correlate with, and may be deduced from, the identity of the host target genes which VGAM733 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29178] Nucleotide sequences of the VGAM733 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM733 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM733 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM733 are further described hereinbelow with reference to Table 1.

[29179] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM733 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM733 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29180] As mentioned hereinabove with reference to Fig. 1, a function of VGAM733 gene, herein designated VGAM is inhibition of expression of VGAM733 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM733 correlate with, and may be deduced from, the identity of the target genes which VGAM733 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29181] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3 (ABCC3, Accession NM\_020038) is a VGAM733 host target gene. ABCC3 BINDING SITE1 and ABCC3 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABCC3, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCC3 BINDING SITE1 and ABCC3 BINDING SITE2, designated SEQ ID:21290 and SEQ ID:21289 respectively, to the nucleotide sequence of VGAM733 RNA, herein designated VGAM RNA, also designated SEQ ID:3444.

[29182] A function of VGAM733 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3 (ABCC3, Accession NM\_020038), a gene which may act as an inducible transporter in the biliary and intestinal excretion of organic anions. Accordingly, utilities of VGAM733 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCC3. The function of ABCC3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM505. Parkinson Disease (autosomal recessive, juvenile) 2, Parkin (PARK2, Accession NM\_004562) is another VGAM733 host target gene. PARK2 BINDING SITE1 through PARK2 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PARK2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PARK2 BINDING SITE1 through PARK2 BINDING SITE3, designated SEQ ID:10905, SEQ ID:15152 and SEQ ID:15159 respectively, to the nucleotide sequence of VGAM733 RNA, herein designated VGAM RNA, also designated SEQ ID:3444.

[29183] Another function of VGAM733 is therefore inhibition of Parkinson Disease (autosomal recessive, juvenile) 2, Parkin (PARK2, Accession NM\_004562). Accordingly, utilities of VGAM733 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PARK2. Olfactomedin 3 (OLFM3, Accession XM\_088951) is another VGAM733 host target gene. OLFM3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OLFM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OLFM3 BINDING SITE, designated SEQ ID:39961, to the nucleotide sequence of VGAM733 RNA, herein designated VGAM RNA, also designated SEQ ID:3444.

[29184] Another function of VGAM733 is therefore inhibition of Olfactomedin 3 (OLFM3, Accession XM\_088951). Accordingly, utilities of VGAM733 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OLFM3. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 734 (VGAM734) viral gene, which

modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29185] VGAM734 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM734 was detected is described hereinabove with reference to Figs. 1–8.

[29186] VGAM734 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Barley Yellow Mosaic Virus. VGAM734 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29187] VGAM734 gene encodes a VGAM734 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM734 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM734 precursor RNA is designated SEQ ID:720, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:720 is located at position 4284 relative to the genome of Barley Yellow Mosaic Virus.

[29188] VGAM734 precursor RNA folds onto itself, forming

VGAM734 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29189] An enzyme complex designated DICER COMPLEX, `dices` the VGAM734 folded precursor RNA into VGAM734 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM734 RNA is designated SEQ ID:3445, and is provided hereinbelow with reference to the sequence listing part.

[29190] VGAM734 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM734 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM734 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29191] VGAM734 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM734 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM734 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM734 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM734 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29192] The complementary binding of VGAM734 RNA, herein designated VGAM RNA, to host target binding sites on VGAM734 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM734 host target RNA into VGAM734 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29193] It is appreciated that VGAM734 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM734 host target genes. The mRNA of each one of this plurality of VGAM734 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM734 RNA, herein designated VGAM RNA, and which when bound by VGAM734 RNA causes inhibition of translation of respective one or more VGAM734 host target proteins.

[29194] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM734 gene, herein designated VGAM GENE, on one or more VGAM734 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29195] It is yet further appreciated that a function of VGAM734 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of viral infection by Barley Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM734 correlate with, and may be deduced from, the identity of the host target genes which VGAM734 binds and inhibits,



and the function of these host target genes, as elaborated hereinbelow.

[29196] Nucleotide sequences of the VGAM734 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM734 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM734 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM734 are further described hereinbelow with reference to Table 1.

[29197] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM734 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM734 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29198] As mentioned hereinabove with reference to Fig. 1, a function of VGAM734 gene, herein designated VGAM is inhibition of expression of VGAM734 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM734 correlate with, and may be deduced from, the identity of the target genes which VGAM734 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[29199] APPL (Accession NM\_012096) is a VGAM734 host target gene. APPL BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by APPL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APPL BINDING SITE, designated SEQ ID:14399, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29200] A function of VGAM734 is therefore inhibition of APPL (Accession NM\_012096). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APPL. Protein Phosphatase 3 (formerly 2B), Catalytic Subunit, Beta Isoform (calcineurin A beta) (PPP3CB, Accession NM\_021132) is another VGAM734 host target gene. PPP3CB BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PPP3CB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP3CB BINDING SITE, designated SEQ

ID:22104, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29201] Another function of VGAM734 is therefore inhibition of Protein Phosphatase 3 (formerly 2B), Catalytic Subunit, Beta Isoform (calcineurin A beta) (PPP3CB, Accession NM\_021132), a gene which is the catalytic subunit of calmodulin-stimulated protein phosphatase 3. Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP3CB. The function of PPP3CB has been established by previous studies. See 114105. Guerini et al. (1989) identified and cloned human cDNA for the Ca(2+)-binding subunit of calcineurin, the brain isozyme of the Ca(2+)/calmodulin-stimulated protein phosphatase. The 2.5-kb cDNA had an open reading frame of 510 bp, a leader sequence of at least 500 bp, and a 1,277-bp 3-prime-noncoding sequence. As was observed with protein levels, mRNA abundance in brain was 20 to 60 times that found in other tissues with the exception of HeLa cells which, like brain, contained abundant calcineurin B mRNA. Animal model experiments lend further support to the function of PPP3CB. In cardiomyocytes, cal-

calcineurin signaling has been implicated in the regulation of the hypertrophic response caused by pressure overload or neuroendocrine stimulation. Bueno et al. (2002) evaluated the necessary function of calcineurin as a hypertrophic regulatory factor by disrupting 1 of the 3 genes that encode the catalytic subunit, calcineurin A-beta, in the mouse. Calcineurin A-beta-deficient mice were viable, fertile, and overtly normal into adulthood, but displayed an 80% decrease in calcineurin enzymatic activity in the heart that was associated with a 12% reduction in basal heart size. Deficient mice were dramatically impaired in their ability to mount a productive hypertrophic response induced by pressure overload, angiotensin II (OMIM Ref. No. 300034) infusion, or isoproterenol infusion. Analysis of marker genes associated with the hypertrophic response revealed a partial defect in the molecular program of hypertrophy. Collectively, these data solidified the hypothesis that calcineurin functions as a central regulator of the cardiac hypertrophic growth response in vivo.

[29202] It is appreciated that the abovementioned animal model for PPP3CB is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[29203] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29204] Guerini, D.; Krinks, M. H.; Sikela, J. M.; Hahn, W. E.; Klee, C. B. : Isolation and sequence of a cDNA clone for human calcineurin B, the  $\text{Ca}(2+)$ -binding subunit of the  $\text{Ca}(2+)$ /calmodulin-stimulated protein phosphatase. DNA 8: 675-682, 1989. ; and

[29205] Bueno, O. F.; Wilkins, B. J.; Tymitz, K. M.; Glascock, B. J.; Kimball, T. F.; Lorenz, J. N.; Molkentin, J. D. : Impaired cardiac hypertrophic response in calcineurin A-beta-deficient mic.

[29206] Further studies establishing the function and utilities of PPP3CB are found in John Hopkins OMIM database record ID 114106, and in cited publications numbered 469 and 4691-4692 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ARPP-19 (Accession NM\_006628) is another VGAM734 host target gene. ARPP-19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARPP-19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of ARPP-19 BINDING SITE, designated SEQ ID:13423, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29207] Another function of VGAM734 is therefore inhibition of ARPP-19 (Accession NM\_006628). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARPP-19. Chromosome 20 Open Reading Frame 26 (C20orf26, Accession XM\_046598) is another VGAM734 host target gene. C20orf26 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C20orf26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf26 BINDING SITE, designated SEQ ID:34758, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29208] Another function of VGAM734 is therefore inhibition of Chromosome 20 Open Reading Frame 26 (C20orf26, Accession XM\_046598). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with C20orf26. Claudin 1 (CLDN1, Accession NM\_021101) is another VGAM734 host target gene. CLDN1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CLDN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLDN1 BINDING SITE, designated SEQ ID:22081, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29209] Another function of VGAM734 is therefore inhibition of Claudin 1 (CLDN1, Accession NM\_021101). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLDN1. FLJ12697 (Accession XM\_166526) is another VGAM734 host target gene. FLJ12697 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12697, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12697 BINDING SITE, designated SEQ ID:44472, to the nucleotide

sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29210] Another function of VGAM734 is therefore inhibition of FLJ12697 (Accession XM\_166526). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12697. FLJ14154 (Accession NM\_024845) is another VGAM734 host target gene. FLJ14154 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14154, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14154 BINDING SITE, designated SEQ ID:24270, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29211] Another function of VGAM734 is therefore inhibition of FLJ14154 (Accession NM\_024845). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14154. ICAP-1A (Accession NM\_004763) is another VGAM734 host target gene. ICAP-1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA



encoded by ICAP-1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ICAP-1A BINDING SITE, designated SEQ ID:11155, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29212] Another function of VGAM734 is therefore inhibition of ICAP-1A (Accession NM\_004763). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ICAP-1A. KIAA0186 (Accession NM\_021067) is another VGAM734 host target gene. KIAA0186 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0186, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0186 BINDING SITE, designated SEQ ID:22037, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29213] Another function of VGAM734 is therefore inhibition of KIAA0186 (Accession NM\_021067). Accordingly, utilities

of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0186. KIAA0527 (Accession XM\_171054) is another VGAM734 host target gene. KIAA0527 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0527, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0527 BINDING SITE, designated SEQ ID:45848, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29214] Another function of VGAM734 is therefore inhibition of KIAA0527 (Accession XM\_171054). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0527. MGC15438 (Accession NM\_032874) is another VGAM734 host target gene. MGC15438 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC15438, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

MGC15438 BINDING SITE, designated SEQ ID:26692, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29215] Another function of VGAM734 is therefore inhibition of MGC15438 (Accession NM\_032874). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15438. poly(A) Polymerase Gamma (PAPOLG, Accession NM\_022894) is another VGAM734 host target gene. PAPOLG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAPOLG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAPOLG BINDING SITE, designated SEQ ID:23155, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29216] Another function of VGAM734 is therefore inhibition of poly(A) Polymerase Gamma (PAPOLG, Accession NM\_022894). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAPOLG. LOC161742

(Accession XM\_091095) is another VGAM734 host target gene. LOC161742 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC161742, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161742 BINDING SITE, designated SEQ ID:40027, to the nucleotide sequence of VGAM734 RNA, herein designated VGAM RNA, also designated SEQ ID:3445.

[29217] Another function of VGAM734 is therefore inhibition of LOC161742 (Accession XM\_091095). Accordingly, utilities of VGAM734 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161742. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 735 (VGAM735) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29218] VGAM735 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM735 was detected is described hereinabove with reference to Figs. 1–8.

[29219] VGAM735 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Barley Yellow Mosaic Virus. VGAM735 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29220] VGAM735 gene encodes a VGAM735 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM735 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM735 precursor RNA is designated SEQ ID:721, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:721 is located at position 755 relative to the genome of Barley Yellow Mosaic Virus.

[29221] VGAM735 precursor RNA folds onto itself, forming VGAM735 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29222] An enzyme complex designated DICER COMPLEX, `dices` the VGAM735 folded precursor RNA into VGAM735 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM735 RNA is designated SEQ ID:3446, and is provided hereinbelow with reference to the sequence listing part.

[29223] VGAM735 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM735 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM735 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29224] VGAM735 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM735 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM735 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM735 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM735 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[29225] The complementary binding of VGAM735 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM735 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM735 host target RNA into VGAM735 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29226] It is appreciated that VGAM735 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM735 host target genes. The mRNA of each one of this plurality of VGAM735 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM735 RNA, herein designated VGAM RNA, and which when bound by VGAM735 RNA causes inhibition of translation of respective one or more VGAM735 host target proteins.

[29227] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM735 gene, herein designated VGAM GENE, on one or more VGAM735 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove



with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29228] It is yet further appreciated that a function of VGAM735 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM735 include diagnosis, prevention and treatment of viral infection by Barley Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM735 correlate with, and may be deduced from, the identity of the host target genes which VGAM735 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29229] Nucleotide sequences of the VGAM735 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM735 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM735 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM735 are further described hereinbelow with reference to Table 1.

[29230] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM735 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM735 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29231] As mentioned hereinabove with reference to Fig. 1, a function of VGAM735 gene, herein designated VGAM is inhibition of expression of VGAM735 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM735 correlate with, and may be deduced from, the identity of the target genes which VGAM735 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29232] SH2 Domain Containing Phosphatase Anchor Protein 1 (SPAP1, Accession NM\_030764) is a VGAM735 host target gene. SPAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

SPAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPAP1 BINDING SITE, designated SEQ ID:25047, to the nucleotide sequence of VGAM735 RNA, herein designated VGAM RNA, also designated SEQ ID:3446.

[29233] A function of VGAM735 is therefore inhibition of SH2 Domain Containing Phosphatase Anchor Protein 1 (SPAP1, Accession NM\_030764), a gene which regulation of immunologic function. Accordingly, utilities of VGAM735 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPAP1. The function of SPAP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM672. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 736 (VGAM736) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29234] VGAM736 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM736 was detected is described hereinabove with reference to Figs. 1–8.

[29235] VGAM736 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Barley Yellow Mosaic Virus. VGAM736 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29236] VGAM736 gene encodes a VGAM736 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM736 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM736 precursor RNA is designated SEQ ID:722, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:722 is located at position 3609 relative to the genome of Barley Yellow Mosaic Virus.

[29237] VGAM736 precursor RNA folds onto itself, forming VGAM736 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29238] An enzyme complex designated DICER COMPLEX, `dices` the VGAM736 folded precursor RNA into VGAM736 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM736 RNA is designated SEQ ID:3447, and is provided hereinbelow with reference to the sequence listing part.

[29239] VGAM736 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM736 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM736 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29240] VGAM736 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM736 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM736 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM736 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM736 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29241] The complementary binding of VGAM736 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM736 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM736 host target RNA into VGAM736 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29242] It is appreciated that VGAM736 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM736 host target genes. The mRNA of each one of this plurality of VGAM736 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM736 RNA, herein designated VGAM RNA, and which when bound by VGAM736 RNA causes inhibition of translation of respective one or more VGAM736 host target proteins.

[29243] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM736 gene, herein designated VGAM GENE, on one or more VGAM736 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29244] It is yet further appreciated that a function of VGAM736 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM736 include diagnosis, prevention and treatment of viral infection by Barley Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM736 correlate with, and may be deduced from, the identity of the host target genes which VGAM736 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29245] Nucleotide sequences of the VGAM736 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the



5`diced` VGAM736 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM736 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM736 are further described hereinbelow with reference to Table 1.

[29246] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM736 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM736 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29247] As mentioned hereinabove with reference to Fig. 1, a function of VGAM736 gene, herein designated VGAM is inhibition of expression of VGAM736 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM736 correlate with, and may be deduced from, the identity of the target genes which VGAM736 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29248] Tensin (TNS, Accession NM\_022648) is a VGAM736 host target gene. TNS BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded

by TNS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNS BINDING SITE, designated SEQ ID:22899, to the nucleotide sequence of VGAM736 RNA, herein designated VGAM RNA, also designated SEQ ID:3447.

[29249] A function of VGAM736 is therefore inhibition of Tensin (TNS, Accession NM\_022648). Accordingly, utilities of VGAM736 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNS. FLJ21438 (Accession XM\_029084) is another VGAM736 host target gene. FLJ21438 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ21438, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21438 BINDING SITE, designated SEQ ID:30844, to the nucleotide sequence of VGAM736 RNA, herein designated VGAM RNA, also designated SEQ ID:3447.

[29250] Another function of VGAM736 is therefore inhibition of FLJ21438 (Accession XM\_029084). Accordingly, utilities of

VGAM736 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21438. KIAA1036 (Accession NM\_014909) is another VGAM736 host target gene. KIAA1036 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1036, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1036 BINDING SITE, designated SEQ ID:17128, to the nucleotide sequence of VGAM736 RNA, herein designated VGAM RNA, also designated SEQ ID:3447.

[29251] Another function of VGAM736 is therefore inhibition of KIAA1036 (Accession NM\_014909). Accordingly, utilities of VGAM736 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1036. KIAA1950 (Accession XM\_166532) is another VGAM736 host target gene. KIAA1950 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1950, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1950 BINDING SITE, designated SEQ ID:44488, to the nucleotide sequence of VGAM736 RNA, herein designated VGAM RNA, also designated SEQ ID:3447.

[29252] Another function of VGAM736 is therefore inhibition of KIAA1950 (Accession XM\_166532). Accordingly, utilities of VGAM736 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1950. MGC19556 (Accession NM\_033551) is another VGAM736 host target gene. MGC19556 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC19556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC19556 BINDING SITE, designated SEQ ID:27314, to the nucleotide sequence of VGAM736 RNA, herein designated VGAM RNA, also designated SEQ ID:3447.

[29253] Another function of VGAM736 is therefore inhibition of MGC19556 (Accession NM\_033551). Accordingly, utilities of VGAM736 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC19556. LOC254428 (Accession XM\_170932) is another VGAM736 host target gene. LOC254428 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254428 BINDING SITE, designated SEQ ID:45714, to the nucleotide sequence of VGAM736 RNA, herein designated VGAM RNA, also designated SEQ ID:3447.

[29254] Another function of VGAM736 is therefore inhibition of LOC254428 (Accession XM\_170932). Accordingly, utilities of VGAM736 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254428. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 737 (VGAM737) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29255] VGAM737 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM737 was detected is described hereinabove with reference to Figs. 1-8.

[29256] VGAM737 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Barley Yellow Mosaic Virus. VGAM737 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29257] VGAM737 gene encodes a VGAM737 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM737 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM737 precursor RNA is designated SEQ ID:723, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:723 is located at position 2030 relative to the genome of Barley Yellow Mosaic Virus.

[29258] VGAM737 precursor RNA folds onto itself, forming VGAM737 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[29259] An enzyme complex designated DICER COMPLEX, `dices` the VGAM737 folded precursor RNA into VGAM737 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 63%) nucleotide sequence of VGAM737 RNA is designated SEQ ID:3448, and is provided hereinbelow with reference to the sequence listing part.

[29260] VGAM737 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM737 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM737 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29261] VGAM737 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM737 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM737 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM737 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM737 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29262] The complementary binding of VGAM737 RNA, herein designated VGAM RNA, to host target binding sites on VGAM737 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and



BINDING SITE III, inhibits translation of VGAM737 host target RNA into VGAM737 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29263] It is appreciated that VGAM737 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM737 host target genes. The mRNA of each one of this plurality of VGAM737 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM737 RNA, herein designated VGAM RNA, and which when bound by VGAM737 RNA causes inhibition of translation of respective one or more VGAM737 host target proteins.

[29264] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM737 gene, herein designated VGAM GENE, on one or more VGAM737 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29265] It is yet further appreciated that a function of VGAM737 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of viral infection by Barley Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM737 correlate with, and may be deduced from, the identity of the host target genes which VGAM737 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29266] Nucleotide sequences of the VGAM737 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM737 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM737 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM737 are further described hereinbelow with reference to Table 1.

[29267] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM737 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM737 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29268] As mentioned hereinabove with reference to Fig. 1, a function of VGAM737 gene, herein designated VGAM is inhibition of expression of VGAM737 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM737 correlate with, and may be deduced from, the identity of the target genes which VGAM737 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29269] Calpain 2, (m/II) Large Subunit (CAPN2, Accession NM\_001748) is a VGAM737 host target gene. CAPN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAPN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of CAPN2 BINDING SITE, designated SEQ ID:7486, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29270] A function of VGAM737 is therefore inhibition of Calpain 2, (m/II) Large Subunit (CAPN2, Accession NM\_001748). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAPN2. Corticotropin Releasing Hormone Receptor 2 (CRHR2, Accession NM\_001883) is another VGAM737 host target gene. CRHR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRHR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRHR2 BINDING SITE, designated SEQ ID:7609, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29271] Another function of VGAM737 is therefore inhibition of Corticotropin Releasing Hormone Receptor 2 (CRHR2, Accession NM\_001883), a gene which is a corticotropin releasing factor receptor type II. Accordingly, utilities of

VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRHR2. The function of CRHR2 has been established by previous studies. Corticotropin-releasing hormone (CRH; 122560) is a 41-amino acid peptide synthesized in the hypothalamus. It is the principal neuroregulator of the hypothalamic-pituitary-adrenocortical axis and plays an important role in coordinating the endocrine, autonomic, and behavioral responses to stress and immune challenge. Liaw et al. (1996) stated that there are 2 G protein-coupled CRH receptors, CRHR1 (OMIM Ref. No. 122561) and CRHR2, which they termed the CRF2 receptor. The investigators used clones of the rat CRF2 receptor to isolate the human gene from brain and kidney genomic DNA libraries. The gene consists of 12 exons spanning approximately 30 kb. The predicted protein, which is 411 amino acids in length and 70% identical to the CRF1 receptor, contains a putative N-terminal secretory signal sequence and 7 putative transmembrane domains. Liaw et al. (1996) expressed the CRF2 receptor and found that transfected cells responded to the binding of CRH with an increase in intracellular cAMP. Although the rat receptor has 2 alternatively spliced variants, termed CRF2-alpha and CRF2-beta, Liaw et al.

(1996) found no evidence for alternative splicing of the human receptor. Liaw et al. (1996) reported that the pharmacologic profile of this protein was similar to that of the rat CRF2- $\alpha$  protein but distinct from the human CRF1 receptor. Kostich et al. (1998) reported a novel CRHR2 splice isoform, which they referred to as 'CRF2- $\gamma$ ,' found in human brain. CRF2- $\gamma$  cDNA encodes a 397-amino acid receptor containing an amino terminus with no significant homology to the already reported  $\alpha$ - and  $\beta$ -termini. PCR and Southern blot analysis of CRF2- $\gamma$  RNA expression in human brain detected expression in the septum and hippocampus, with weaker but detectable expression in the amygdala, nucleus accumbens, midbrain, and frontal cortex. Animal model experiments lend further support to the function of CRHR2. Kishimoto et al. (2000) generated mice deficient for *Crhr2* by targeted disruption. They reported that male but not female *Crhr2*-deficient mice exhibited enhanced anxious behavior in several tests of anxiety in contrast to mice lacking *Crhr1*. The enhanced anxiety of *Crhr2*-deficient mice was not due to changes in hypothalamic-pituitary-adrenal axis activity, but rather reflected impaired responses in specific brain regions involved in emotional

and autonomic functions, as monitored by a reduction in Creb phosphorylation in male, but not female, *Crhr2*  $-/-$  mice. Kishimoto et al. (2000) proposed that CRHR1 predominantly mediates a central anxiolytic response, opposing the general anxiogenic effect of CRH mediated by CRHR1. Kishimoto et al. (2000) found that neither male nor female *Crhr2*-deficient mice showed alterations of baseline feeding behavior. Both responded with increased edema formation in response to thermal exposure, however, indicating that in contrast to its central role in anxiety, the peripheral role of CRHR2 in vascular permeability is independent of gender.

[29272] It is appreciated that the abovementioned animal model for CRHR2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[29273] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29274] Kostich, W. A.; Chen, A.; Sperle, K.; Largent, B. L. : Molecular identification and analysis of a novel human corticotropin-releasing factor (CRF) receptor: the CRF2-gamma receptor. *Molec. Endocr.* 12: 1077-1085,

1998. ; and

[29275] Kishimoto, T.; Radulovic, J.; Radulovic, M.; Lin, C. R.; Schrick, C.; Hooshmand, F.; Hermanson, O.; Rosenfeld, M. G.; Spiess, J. : Deletion of Crhr2 reveals an anxiolytic role for cortic.

[29276] Further studies establishing the function and utilities of CRHR2 are found in John Hopkins OMIM database record ID 602034, and in cited publications numbered 943-94 and 1988-950 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Muscleblind-like (Drosophila) (MBNL, Accession NM\_021038) is another VGAM737 host target gene. MBNL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MBNL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MBNL BINDING SITE, designated SEQ ID:22030, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29277] Another function of VGAM737 is therefore inhibition of Muscleblind-like (Drosophila) (MBNL, Accession NM\_021038), a gene which binds to cug triplet repeat ex-



pansion dsrna (by similarity). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBNL. The function of MBNL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM95. MADS Box Transcription Enhancer Factor 2, Polypeptide C (myocyte enhancer factor 2C) (MEF2C, Accession NM\_002397) is another VGAM737 host target gene. MEF2C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MEF2C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEF2C BINDING SITE, designated SEQ ID:8212, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29278] Another function of VGAM737 is therefore inhibition of MADS Box Transcription Enhancer Factor 2, Polypeptide C (myocyte enhancer factor 2C) (MEF2C, Accession NM\_002397), a gene which regulates muscle-specific and mitogen-inducible genes. Accordingly, utilities of

VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEF2C. The function of MEF2C and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM386.8-oxoguanine DNA Glycosylase (OGG1, Accession NM\_002542) is another VGAM737 host target gene. OGG1 BINDING SITE1 through OGG1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by OGG1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OGG1 BINDING SITE1 through OGG1 BINDING SITE3, designated SEQ ID:8393, SEQ ID:18810 and SEQ ID:18815 respectively, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29279] Another function of VGAM737 is therefore inhibition of 8-oxoguanine DNA Glycosylase (OGG1, Accession NM\_002542), a gene which is involved in base excision DNA repair and removal of 8-oxyguanine. Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with OGG1. The function of OGG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM390. Phosphotriesterase Related (PTER, Accession NM\_030664) is another VGAM737 host target gene. PTER BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTER, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTER BINDING SITE, designated SEQ ID:24999, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29280] Another function of VGAM737 is therefore inhibition of Phosphotriesterase Related (PTER, Accession NM\_030664), a gene which is a phosphotriesterase homology protein. Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTER. The function of PTER and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM713. Retinoic Acid Receptor, Beta (RARβ, Accession NM\_016152) is another

VGAM737 host target gene. RARB BINDING SITE1 and RARB BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RARB, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RARB BINDING SITE1 and RARB BINDING SITE2, designated SEQ ID:18239 and SEQ ID:6693 respectively, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29281] Another function of VGAM737 is therefore inhibition of Retinoic Acid Receptor, Beta (RARB, Accession NM\_016152), a gene which is one member of the steroid/thyroid hormone receptor family of ligand-activated transcription factors. Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RARB. The function of RARB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. Thioredoxin Interacting Protein (TXNIP, Accession NM\_006472) is another VGAM737 host target gene. TXNIP BINDING SITE is HOST TARGET binding site found in

the 3' untranslated region of mRNA encoded by TXNIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TXNIP BINDING SITE, designated SEQ ID:13196, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29282] Another function of VGAM737 is therefore inhibition of Thioredoxin Interacting Protein (TXNIP, Accession NM\_006472), a gene which binds and inhibits thioredoxin, a major regulator of cellular redox state. Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TXNIP. The function of TXNIP has been established by previous studies. Exposure to vitamin D3 (1,25-dihydroxyvitamin D3) or phorbol ester induces the bipotent HL-60 cell promyelocytic leukemia cell line to differentiate into monocytes/macrophages, whereas retinoic acid and dimethylsulfoxide induce differentiation towards granulocytes. The differentiation is accompanied by regulation of MYC (OMIM Ref. No. 190080), FOS (OMIM Ref. No. 164810), FMS (CSF1R; 164770), and myeloblastin (PRTN3; 177020). By differential screening of HL60 cell

lines, Chen and DeLuca (1994) identified a cDNA encoding TXNIP, which they termed VDUP1. The deduced TXNIP protein has 391 amino acids. Ribonuclease protection analysis showed dramatically increased expression of TXNIP in response to vitamin D3 but not to phorbol ester. Chen and DeLuca (1994) concluded that TXNIP is not involved in the differentiation process. Familial combined hyperlipidemia (OMIM Ref. No. 144250) is a common, multifactorial and heterogeneous dyslipidemia predisposing to premature coronary artery disease and characterized by elevated plasma triglycerides, cholesterol, or both. Castellani et al. (1998) identified a mouse mutant strain, HcB-19, that shares features with familial combined hyperlipidemia, including hypertriglyceridemia, hypercholesterolemia, elevated plasma apolipoprotein B, and increased secretion of triglyceride-rich lipoproteins. This disorder was shown to result from spontaneous mutation at a locus, designated Hyplip1, on distal mouse chromosome 3 in a region syntenic to 1q21-q23, where a locus for familial combined hyperlipidemia was identified in Finnish, German, Chinese, and U.S. families. By positional cloning, Bodnar et al. (2002) demonstrated that the Hyplip1 gene is Txnip, and they demonstrated a Txnip non-

sense mutation in the HcB-19 strain that was absent in its normolipidemic parental strains. Txnip encodes a cytoplasmic protein that binds and inhibits thioredoxin, a major regulator of cellular redox state. The mutant mice showed a decreased flux of fatty acids through the TCA cycle, resulting in increased availability for ketogenesis and triglyceride synthesis. The authors suggested further studies to elucidate the potential role of the human homolog in familial combined hyperlipidemia and other metabolic disorder

[29283] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29284] Chen, K.-S.; DeLuca, H. F. : Isolation and characterization of a novel cDNA from HL-60 cells treated with 1,25-dihydroxyvitamin D-3. *Biochim. Biophys. Acta* 1219: 26-32, 1994. ; and

[29285] Bodnar, J. S.; Chatterjee, A.; Castellani, L. W.; Ross, D. A.; Ohmen, J.; Cavalcoli, J.; Wu, C.; Dains, K. M.; Catanese, J.; Chu, M.; Sheth, S. S.; Charugundla, K.; Demant, P.; West, D. B.;.

[29286] Further studies establishing the function and utilities of TXNIP are found in John Hopkins OMIM database record ID

606599, and in cited publications numbered 103 and 4515–4516 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0935 (Accession XM\_052620) is another VGAM737 host target gene. KIAA0935 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0935, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0935 BINDING SITE, designated SEQ ID:36013, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29287] Another function of VGAM737 is therefore inhibition of KIAA0935 (Accession XM\_052620). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0935. KIAA0937 (Accession XM\_166213) is another VGAM737 host target gene. KIAA0937 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0937, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the



complementarity of the nucleotide sequences of KIAA0937 BINDING SITE, designated SEQ ID:44019, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29288] Another function of VGAM737 is therefore inhibition of KIAA0937 (Accession XM\_166213). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0937. KIAA1303 (Accession XM\_038376) is another VGAM737 host target gene. KIAA1303 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1303, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1303 BINDING SITE, designated SEQ ID:32831, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29289] Another function of VGAM737 is therefore inhibition of KIAA1303 (Accession XM\_038376). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1303. OS-9 (Accession NM\_006812) is another

VGAM737 host target gene. OS-9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OS-9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OS-9 BINDING SITE, designated SEQ ID:13683, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29290] Another function of VGAM737 is therefore inhibition of OS-9 (Accession NM\_006812). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OS-9. Sideroflexin 2 (SFXN2, Accession XM\_058359) is another VGAM737 host target gene. SFXN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFXN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFXN2 BINDING SITE, designated SEQ ID:36601, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29291] Another function of VGAM737 is therefore inhibition of Sideroflexin 2 (SFXN2, Accession XM\_058359). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFXN2. Smith–Magenis Syndrome Chromosome Region, Candidate 5 (SMCR5, Accession NM\_144774) is another VGAM737 host target gene. SMCR5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SMCR5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMCR5 BINDING SITE, designated SEQ ID:29565, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29292] Another function of VGAM737 is therefore inhibition of Smith–Magenis Syndrome Chromosome Region, Candidate 5 (SMCR5, Accession NM\_144774). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMCR5. Signal Sequence Receptor, Alpha (translocon–associated protein alpha) (SSR1, Accession NM\_003144) is another VGAM737 host target gene. SSR1 BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by SSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSR1 BINDING SITE, designated SEQ ID:9112, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29293] Another function of VGAM737 is therefore inhibition of Signal Sequence Receptor, Alpha (translocon-associated protein alpha) (SSR1, Accession NM\_003144). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSR1. Syntaxin 3A (STX3A, Accession NM\_004177) is another VGAM737 host target gene. STX3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STX3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STX3A BINDING SITE, designated SEQ ID:10388, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29294] Another function of VGAM737 is therefore inhibition of Syntaxin 3A (STX3A, Accession NM\_004177). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STX3A. LOC149842 (Accession XM\_097745) is another VGAM737 host target gene. LOC149842 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149842, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149842 BINDING SITE, designated SEQ ID:41091, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29295] Another function of VGAM737 is therefore inhibition of LOC149842 (Accession XM\_097745). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149842. LOC221143 (Accession XM\_167986) is another VGAM737 host target gene. LOC221143 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221143, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221143 BINDING SITE, designated SEQ ID:44944, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29296] Another function of VGAM737 is therefore inhibition of LOC221143 (Accession XM\_167986). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221143. LOC254394 (Accession XM\_171127) is another VGAM737 host target gene. LOC254394 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254394, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254394 BINDING SITE, designated SEQ ID:45930, to the nucleotide sequence of VGAM737 RNA, herein designated VGAM RNA, also designated SEQ ID:3448.

[29297] Another function of VGAM737 is therefore inhibition of LOC254394 (Accession XM\_171127). Accordingly, utilities of VGAM737 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC254394. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 738 (VGAM738) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29298] VGAM738 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM738 was detected is described hereinabove with reference to Figs. 1–8.

[29299] VGAM738 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Barley Yellow Mosaic Virus. VGAM738 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29300] VGAM738 gene encodes a VGAM738 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM738 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM738 precursor RNA is designated SEQ ID:724, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:724 is located at position 3974 relative to the genome of Barley Yellow Mosaic Virus.

[29301] VGAM738 precursor RNA folds onto itself, forming VGAM738 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29302] An enzyme complex designated DICER COMPLEX, `dices` the VGAM738 folded precursor RNA into VGAM738 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM738 RNA is designated SEQ ID:3449, and is provided hereinbelow with reference to the sequence listing part.



[29303] VGAM738 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM738 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM738 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29304] VGAM738 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM738 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM738 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM738 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM738 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[29305] The complementary binding of VGAM738 RNA, herein designated VGAM RNA, to host target binding sites on VGAM738 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM738 host target RNA into VGAM738 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29306] It is appreciated that VGAM738 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM738 host target genes. The mRNA of each one of this plurality of VGAM738 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM738 RNA, herein designated VGAM RNA, and which when bound by VGAM738 RNA causes in-

hibition of translation of respective one or more VGAM738 host target proteins.

[29307] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM738 gene, herein designated VGAM GENE, on one or more VGAM738 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29308] It is yet further appreciated that a function of VGAM738 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM738 include diagnosis, prevention and

treatment of viral infection by Barley Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM738 correlate with, and may be deduced from, the identity of the host target genes which VGAM738 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [29309] Nucleotide sequences of the VGAM738 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM738 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM738 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM738 are further described hereinbelow with reference to Table 1.
- [29310] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM738 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM738 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [29311] As mentioned hereinabove with reference to Fig. 1, a function of VGAM738 gene, herein designated VGAM is inhibition of expression of VGAM738 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM738 correlate with, and may be deduced from, the identity of the target genes which VGAM738 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29312] Ecotropic Viral Integration Site 2A (EVI2A, Accession NM\_014210) is a VGAM738 host target gene. EVI2A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EVI2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVI2A BINDING SITE, designated SEQ ID:15477, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29313] A function of VGAM738 is therefore inhibition of Ecotropic Viral Integration Site 2A (EVI2A, Accession NM\_014210), a gene which may complex with itself or/and other proteins within the membrane, to function as part of a cell-surface receptor. Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EVI2A. The function of EVI2A has been established by previous studies. O'Connell et al.

(1989, 1990) demonstrated by genetic linkage and by somatic cell hybrid and pulsed field gel electrophoresis that EVI2, the human homolog of the mouse myeloid leukemia-associated gene Evi2, maps between 2 breakpoints on the proximal part of 17q that define the location of the gene for neurofibromatosis (OMIM Ref. No. 162200). Sequencing studies predicted an EVI2 protein of 232 amino acids and structural features consistent with the view that EVI2 is a membrane protein that may complex with itself and/or other proteins within the membrane, perhaps to function as part of a cell-surface receptor. In the course of these studies of the structure of the EVI2 gene, Cawthon et al. (1990) identified 2 other transcripts that map between the NF1 translocation breakpoints. Collins (1993) symbolized this gene EVDA.

[29314] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29315] O'Connell, P.; Viskochil, D.; Buchberg, A. M.; Fountain, J.; Cawthon, R. M.; Culver, M.; Stevens, J.; Rich, D. C.; Ledbetter, D. H.; Wallace, M.; Carey, J. C.; Jenkins, N. A.; Copeland, N. G.; Collins, F. S.; White, R. : The human homolog of murine Evi-2 lies between two von Reckling-

hausen neurofibromatosis translocations. Genomics 7: 547–554, 1990. ; and

[29316] Cawthon, R. M.; O'Connell, P.; Buchberg, A. M.; Viskochil, D.; Weiss, R. B.; Culver, M.; Stevens, J.; Jenkins, N. A.; Copeland, N. G.; White, R. : Identification and characterization of.

[29317] Further studies establishing the function and utilities of EVI2A are found in John Hopkins OMIM database record ID 158380, and in cited publications numbered 3803–3806 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RecQ Protein–like 5 (RECQL5, Accession NM\_004259) is another VGAM738 host target gene. RECQL5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RECQL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RECQL5 BINDING SITE, designated SEQ ID:10446, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29318] Another function of VGAM738 is therefore inhibition of RecQ Protein–like 5 (RECQL5, Accession NM\_004259). Ac–

cordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RECQL5. Thrombospondin 1 (THBS1, Accession NM\_003246) is another VGAM738 host target gene. THBS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by THBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of THBS1 BINDING SITE, designated SEQ ID:9254, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29319] Another function of VGAM738 is therefore inhibition of Thrombospondin 1 (THBS1, Accession NM\_003246), a gene which is a member of a family of adhesive molecules, involves in blood clotting and in angiogenesis. Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with THBS1. The function of THBS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM20. Ras Homolog Gene Family, Member E (ARHE, Accession NM\_005168) is an-



other VGAM738 host target gene. ARHE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHE BINDING SITE, designated SEQ ID:11666, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29320] Another function of VGAM738 is therefore inhibition of Ras Homolog Gene Family, Member E (ARHE, Accession NM\_005168). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHE. Eukaryotic Translation Initiation Factor 3, Subunit 1 Alpha, 35kDa (EIF3S1, Accession XM\_032384) is another VGAM738 host target gene. EIF3S1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF3S1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF3S1 BINDING SITE, designated SEQ ID:31640, to the nucleotide sequence of VGAM738 RNA,

herein designated VGAM RNA, also designated SEQ ID:3449.

[29321] Another function of VGAM738 is therefore inhibition of Eukaryotic Translation Initiation Factor 3, Subunit 1 Alpha, 35kDa (EIF3S1, Accession XM\_032384). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF3S1. FLJ20330 (Accession NM\_018988) is another VGAM738 host target gene. FLJ20330 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20330, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20330 BINDING SITE, designated SEQ ID:21058, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29322] Another function of VGAM738 is therefore inhibition of FLJ20330 (Accession NM\_018988). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20330. KIAA1432 (Accession XM\_039698) is another VGAM738 host target gene. KIAA1432 BINDING SITE is HOST TARGET

binding site found in the 5' untranslated region of mRNA encoded by KIAA1432, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1432 BINDING SITE, designated SEQ ID:33149, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29323] Another function of VGAM738 is therefore inhibition of KIAA1432 (Accession XM\_039698). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1432. P66 (Accession NM\_020699) is another VGAM738 host target gene. P66 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P66, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P66 BINDING SITE, designated SEQ ID:21847, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29324] Another function of VGAM738 is therefore inhibition of

P66 (Accession NM\_020699). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P66. Phosphatidylinositol-4-phosphate 5-kinase, Type II, Alpha (PIP5K2A, Accession NM\_005028) is another VGAM738 host target gene. PIP5K2A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PIP5K2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIP5K2A BINDING SITE, designated SEQ ID:11469, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29325] Another function of VGAM738 is therefore inhibition of Phosphatidylinositol-4-phosphate 5-kinase, Type II, Alpha (PIP5K2A, Accession NM\_005028). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP5K2A. Testis-specific Transcript, Y-linked 2 (TTY2, Accession XM\_099029) is another VGAM738 host target gene. TTY2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by

TTY2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TTY2 BINDING SITE, designated SEQ ID:42067, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29326] Another function of VGAM738 is therefore inhibition of Testis-specific Transcript, Y-linked 2 (TTY2, Accession XM\_099029). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TTY2. LOC159148 (Accession XM\_099030) is another VGAM738 host target gene. LOC159148 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC159148, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC159148 BINDING SITE, designated SEQ ID:42074, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29327] Another function of VGAM738 is therefore inhibition of

LOC159148 (Accession XM\_099030). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC159148. LOC221718 (Accession XM\_168062) is another VGAM738 host target gene. LOC221718 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221718, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221718 BINDING SITE, designated SEQ ID:44981, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29328] Another function of VGAM738 is therefore inhibition of LOC221718 (Accession XM\_168062). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221718. LOC256880 (Accession XM\_173135) is another VGAM738 host target gene. LOC256880 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256880, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC256880 BINDING SITE, designated SEQ ID:46384, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29329] Another function of VGAM738 is therefore inhibition of LOC256880 (Accession XM\_173135). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256880. LOC90246 (Accession XM\_030283) is another VGAM738 host target gene. LOC90246 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90246, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90246 BINDING SITE, designated SEQ ID:31001, to the nucleotide sequence of VGAM738 RNA, herein designated VGAM RNA, also designated SEQ ID:3449.

[29330] Another function of VGAM738 is therefore inhibition of LOC90246 (Accession XM\_030283). Accordingly, utilities of VGAM738 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90246. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 739 (VGAM739) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29331] VGAM739 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM739 was detected is described hereinabove with reference to Figs. 1–8.

[29332] VGAM739 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Taura Syndrome Virus. VGAM739 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29333] VGAM739 gene encodes a VGAM739 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM739 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM739 precursor RNA is designated SEQ ID:725, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:725 is



located at position 4695 relative to the genome of Taura Syndrome Virus.

[29334] VGAM739 precursor RNA folds onto itself, forming VGAM739 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29335] An enzyme complex designated DICER COMPLEX, `dices` the VGAM739 folded precursor RNA into VGAM739 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM739 RNA is designated SEQ ID:3450, and is provided hereinbelow with reference to the sequence listing part.

[29336] VGAM739 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM739 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM739 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[29337] VGAM739 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM739 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM739 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM739 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM739 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[29338] The complementary binding of VGAM739 RNA, herein designated VGAM RNA, to host target binding sites on VGAM739 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM739 host target RNA into VGAM739 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29339] It is appreciated that VGAM739 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM739 host target genes. The mRNA of each one of this plurality of VGAM739 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM739 RNA, herein designated VGAM RNA, and which when bound by VGAM739 RNA causes inhibition of translation of respective one or more VGAM739

host target proteins.

[29340] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM739 gene, herein designated VGAM GENE, on one or more VGAM739 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29341] It is yet further appreciated that a function of VGAM739 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of viral infection by Taura Syndrome Virus. Spe-

cific functions, and accordingly utilities, of VGAM739 correlate with, and may be deduced from, the identity of the host target genes which VGAM739 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29342] Nucleotide sequences of the VGAM739 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM739 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM739 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM739 are further described hereinbelow with reference to Table 1.

[29343] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM739 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM739 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29344] As mentioned hereinabove with reference to Fig. 1, a function of VGAM739 gene, herein designated VGAM is inhibition of expression of VGAM739 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM739 correlate with, and may be deduced from, the identity of the target genes which VGAM739 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29345] Inhibitor of Kappa Light Polypeptide Gene Enhancer In B-cells, Kinase Gamma (IKBKG, Accession NM\_003639) is a VGAM739 host target gene. IKBKG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IKBKG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IKBKG BINDING SITE, designated SEQ ID:9712, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29346] A function of VGAM739 is therefore inhibition of Inhibitor of Kappa Light Polypeptide Gene Enhancer In B-cells, Kinase Gamma (IKBKG, Accession NM\_003639), a gene which regulatory subunit part of the ikk-signalosome complex activation. also considered to be a mediator for tax activation of nf-kappa-b. could be implicated in nf-kappa-b-mediated protection from cytokine toxicity. Accordingly, utilities of VGAM739 include diagnosis, preven-

tion and treatment of diseases and clinical conditions associated with IKBKG. The function of IKBKG and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM471. Mdm4, Transformed 3T3 Cell Double Minute 4, P53 Binding Protein (mouse) (MDM4, Accession NM\_002393) is another VGAM739 host target gene. MDM4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MDM4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MDM4 BINDING SITE, designated SEQ ID:8209, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29347] Another function of VGAM739 is therefore inhibition of Mdm4, Transformed 3T3 Cell Double Minute 4, P53 Binding Protein (mouse) (MDM4, Accession NM\_002393), a gene which Strongly similar to murine Mdm4; may interact with p53. Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MDM4. The function of MDM4

has been established by previous studies. Shvarts et al. (1997) isolated cDNAs encoding MDM4 by screening a human cDNA library from a colonic tumorigenic cell line with a mouse mdmx probe. The human MDM4 gene encodes a 490-amino acid protein containing a RING finger domain and a putative nuclear localization signal. The predicted mass of the protein was 54 kD, while the observed mass was 80 kD, a difference which Shvarts et al. (1997) stated was probably due to phosphorylation or other posttranslational modification. Northern blot analysis revealed a 10-kb mRNA expressed at a high level in thymus and at lower levels in all other tissues tested. A 2.2-kb mRNA was detected in testis. MDM4 protein produced by in vitro translation interacts with p53 (OMIM Ref. No. 191170) via a binding domain located in the N-terminal region of the MDM4 protein. MDM4 shows significant structural similarity to p53-binding protein MDM2 (OMIM Ref. No. 164785), an E3 ubiquitin ligase. The interaction between MDM2 and p53 is critical for cell viability; loss of Mdm2 causes cell death in vitro and in vivo in a p53-dependent manner. MDM4 has some of the same properties as MDM2, but unlike MDM2, it does not cause nuclear export or degradation of p53. To study MDM4 function in vivo,



Parant et al. (2001) deleted the Mdm4 gene in mice. Mdm4-null mice died at 7.5 to 8.5 days postcoitum due to loss of cell proliferation. When Parant et al. (2001) crossed in a p53-null allele, they found that loss of p53 completely rescued the Mdm4 -/- embryonic lethality. Thus, MDM2 and MDM4 are nonoverlapping critical regulators of p53 in vivo. These data defined a new pathway of p53 regulation and raised the possibility that increased MDM4 levels and the resulting inactivation of p53 contribute to the development of human tumors. By fluorescence in situ hybridization, Shvarts et al. (1997) mapped the MDM4 gene to human chromosome 1q32.

[29348] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29349] Parant, J.; Chavez-Reyes, A.; Little, N. A.; Yan, W.; Reinke, V.; Jochemsen, A. G.; Lozano, G. : Rescue of embryonic lethality in Mdm4-null mice by loss of Trp53 suggests a nonoverlapping pathway with MDM2 to regulate p53. *Nature Genet.* 29: 92-95, 2001. ; and

[29350] Shvarts, A.; Bazuine, M.; Dekker, P.; Ramos, Y. F. M.; Steengenga, W. T.; Merckx, G.; van Ham, R. C. A.; van der Hoven van Oordt, W.; van der Eb, A. J.; Jochemsen, A. G. :

Isolation an.

[29351] Further studies establishing the function and utilities of MDM4 are found in John Hopkins OMIM database record ID 602704, and in cited publications numbered 1046–1047 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Phosphatase 2 (formerly 2A), Catalytic Subunit, Alpha Isoform (PPP2CA, Accession NM\_002715) is another VGAM739 host target gene. PPP2CA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2CA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2CA BINDING SITE, designated SEQ ID:8582, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29352] Another function of VGAM739 is therefore inhibition of Protein Phosphatase 2 (formerly 2A), Catalytic Subunit, Alpha Isoform (PPP2CA, Accession NM\_002715), a gene which plays a role in the regulation of most major metabolic pathways. Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with PPP2CA. The function of PPP2CA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM399. Synaptotagmin I (SYT1, Accession NM\_005639) is another VGAM739 host target gene. SYT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SYT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYT1 BINDING SITE, designated SEQ ID:12173, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29353] Another function of VGAM739 is therefore inhibition of Synaptotagmin I (SYT1, Accession NM\_005639), a gene which may have a regulatory role in the membrane interactions during trafficking of synaptic vesicles at the active zone of the synapse. Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYT1. The function of SYT1 has been established by previous studies. Perin et al. (1991) characterized full-length cDNAs encoding hu-

man and *Drosophila* synaptotagmins. Similarity of the phospholipid binding properties of the cytoplasmic domains of rat, human, and *Drosophila* synaptotagmins and selective conservation of the sequences that are homologous to protein kinase C (see OMIM Ref. No. 176960) suggested that these may be involved in phospholipid binding. Neurons release neurotransmitters by calcium-dependent exocytosis of synaptic vesicles. Brose et al. (1992) reported that synaptotagmin, a highly conserved synaptic vesicle protein, binds calcium at physiologic concentrations in a complex with negatively charged phospholipids. This binding is specific for calcium and involves the cytoplasmic domain of synaptotagmin. Calcium binding is dependent on the intact oligomeric structure of synaptotagmin; it is abolished by proteolytic cleavage at a single site. Brose et al. (1992) interpreted the results as suggesting that synaptotagmin acts as a cooperative calcium receptor in exocytosis. Synaptotagmin contains 2 copies of a sequence that is homologous to the regulatory region of protein kinase C (OMIM Ref. No. 176960).

[29354] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29355] Brose, N.; Petrenko, A. G.; Sudhof, T. C.; Jahn, R. : Synaptotagmin: a calcium sensor on the synaptic vesicle surface. Science 256: 1021–1025, 1992. ; and

[29356] Perin, M. S.; Johnston, P. A.; Ozcelik, T.; Jahn, R.; Francke, U.; Sudhof, T. C. : Structural and functional conservation of synaptotagmin (p65) in Drosophila and humans. J. Biol. Chem.

[29357] Further studies establishing the function and utilities of SYT1 are found in John Hopkins OMIM database record ID 185605, and in cited publications numbered 1569–1580 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ22167 (Accession NM\_024533) is another VGAM739 host target gene. FLJ22167 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ22167, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22167 BINDING SITE, designated SEQ ID:23739, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29358] Another function of VGAM739 is therefore inhibition of

FLJ22167 (Accession NM\_024533). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22167. General Transcription Factor IIE, Polypeptide 1, Alpha 56kDa (GTF2E1, Accession NM\_005513) is another VGAM739 host target gene. GTF2E1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by GTF2E1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GTF2E1 BINDING SITE, designated SEQ ID:12039, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29359] Another function of VGAM739 is therefore inhibition of General Transcription Factor IIE, Polypeptide 1, Alpha 56kDa (GTF2E1, Accession NM\_005513). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GTF2E1. KIAA0186 (Accession NM\_021067) is another VGAM739 host target gene. KIAA0186 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0186, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0186 BINDING SITE, designated SEQ ID:22041, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29360] Another function of VGAM739 is therefore inhibition of KIAA0186 (Accession NM\_021067). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0186. KIAA1610 (Accession XM\_040622) is another VGAM739 host target gene. KIAA1610 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1610, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1610 BINDING SITE, designated SEQ ID:33343, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29361] Another function of VGAM739 is therefore inhibition of KIAA1610 (Accession XM\_040622). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1610. PRO2012 (Accession NM\_018614) is another VGAM739 host target gene. PRO2012 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRO2012, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2012 BINDING SITE, designated SEQ ID:20683, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29362] Another function of VGAM739 is therefore inhibition of PRO2012 (Accession NM\_018614). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2012. LOC145758 (Accession XM\_096858) is another VGAM739 host target gene. LOC145758 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145758, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145758 BINDING SITE, designated SEQ ID:40588, to the nucleotide se-



quence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29363] Another function of VGAM739 is therefore inhibition of LOC145758 (Accession XM\_096858). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145758. LOC149506 (Accession XM\_097661) is another VGAM739 host target gene. LOC149506 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149506, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149506 BINDING SITE, designated SEQ ID:41011, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29364] Another function of VGAM739 is therefore inhibition of LOC149506 (Accession XM\_097661). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149506. LOC158014 (Accession XM\_088442) is another VGAM739 host target gene. LOC158014 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC158014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158014 BINDING SITE, designated SEQ ID:39697, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29365] Another function of VGAM739 is therefore inhibition of LOC158014 (Accession XM\_088442). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158014. LOC202316 (Accession XM\_117380) is another VGAM739 host target gene. LOC202316 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202316 BINDING SITE, designated SEQ ID:43428, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29366] Another function of VGAM739 is therefore inhibition of LOC202316 (Accession XM\_117380). Accordingly, utilities

of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202316. LOC254196 (Accession XM\_173220) is another VGAM739 host target gene. LOC254196 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC254196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254196 BINDING SITE, designated SEQ ID:46478, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29367] Another function of VGAM739 is therefore inhibition of LOC254196 (Accession XM\_173220). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254196. LOC90538 (Accession XM\_032401) is another VGAM739 host target gene. LOC90538 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC90538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC90538 BINDING SITE, designated SEQ ID:31661, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29368] Another function of VGAM739 is therefore inhibition of LOC90538 (Accession XM\_032401). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90538. LOC91585 (Accession XM\_039395) is another VGAM739 host target gene. LOC91585 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91585, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91585 BINDING SITE, designated SEQ ID:33078, to the nucleotide sequence of VGAM739 RNA, herein designated VGAM RNA, also designated SEQ ID:3450.

[29369] Another function of VGAM739 is therefore inhibition of LOC91585 (Accession XM\_039395). Accordingly, utilities of VGAM739 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91585. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 740 (VGAM740) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29370] VGAM740 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM740 was detected is described hereinabove with reference to Figs. 1–8.

[29371] VGAM740 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Taura Syndrome Virus. VGAM740 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29372] VGAM740 gene encodes a VGAM740 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM740 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM740 precursor RNA is designated SEQ ID:726, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:726 is located at position 5382 relative to the genome of Taura

Syndrome Virus.

[29373] VGAM740 precursor RNA folds onto itself, forming VGAM740 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29374] An enzyme complex designated DICER COMPLEX, `dices` the VGAM740 folded precursor RNA into VGAM740 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM740 RNA is designated SEQ ID:3451, and is provided hereinbelow with reference to the sequence listing part.

[29375] VGAM740 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM740 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM740 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29376] VGAM740 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM740 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM740 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM740 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM740 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29377] The complementary binding of VGAM740 RNA, herein designated VGAM RNA, to host target binding sites on VGAM740 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM740 host target RNA into VGAM740 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29378] It is appreciated that VGAM740 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM740 host target genes. The mRNA of each one of this plurality of VGAM740 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM740 RNA, herein designated VGAM RNA, and which when bound by VGAM740 RNA causes inhibition of translation of respective one or more VGAM740 host target proteins.



[29379] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM740 gene, herein designated VGAM GENE, on one or more VGAM740 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29380] It is yet further appreciated that a function of VGAM740 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM740 include diagnosis, prevention and treatment of viral infection by Taura Syndrome Virus. Specific functions, and accordingly utilities, of VGAM740 cor-

relate with, and may be deduced from, the identity of the host target genes which VGAM740 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29381] Nucleotide sequences of the VGAM740 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM740 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM740 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM740 are further described hereinbelow with reference to Table 1.

[29382] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM740 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM740 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29383] As mentioned hereinabove with reference to Fig. 1, a function of VGAM740 gene, herein designated VGAM is inhibition of expression of VGAM740 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM740 correlate with, and may be deduced

from, the identity of the target genes which VGAM740 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29384] FLJ13322 (Accession NM\_024722) is a VGAM740 host target gene. FLJ13322 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13322 BINDING SITE, designated SEQ ID:24057, to the nucleotide sequence of VGAM740 RNA, herein designated VGAM RNA, also designated SEQ ID:3451.

[29385] A function of VGAM740 is therefore inhibition of FLJ13322 (Accession NM\_024722). Accordingly, utilities of VGAM740 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13322. MGC9912 (Accession NM\_080664) is another VGAM740 host target gene. MGC9912 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGC9912, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of MGC9912 BINDING SITE, designated SEQ ID:27950, to the nucleotide sequence of VGAM740 RNA, herein designated VGAM RNA, also designated SEQ ID:3451.

[29386] Another function of VGAM740 is therefore inhibition of MGC9912 (Accession NM\_080664). Accordingly, utilities of VGAM740 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC9912. Nuclear Transcription Factor, X-box Binding 1 (NFX1, Accession NM\_002504) is another VGAM740 host target gene. NFX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NFX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFX1 BINDING SITE, designated SEQ ID:8326, to the nucleotide sequence of VGAM740 RNA, herein designated VGAM RNA, also designated SEQ ID:3451.

[29387] Another function of VGAM740 is therefore inhibition of Nuclear Transcription Factor, X-box Binding 1 (NFX1, Accession NM\_002504). Accordingly, utilities of VGAM740 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with NFX1. Ribosomal Protein S6 Kinase, 90kDa, Polypeptide 4 (RPS6KA4, Accession NM\_003942) is another VGAM740 host target gene. RPS6KA4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RPS6KA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RPS6KA4 BINDING SITE, designated SEQ ID:10056, to the nucleotide sequence of VGAM740 RNA, herein designated VGAM RNA, also designated SEQ ID:3451.

[29388] Another function of VGAM740 is therefore inhibition of Ribosomal Protein S6 Kinase, 90kDa, Polypeptide 4 (RPS6KA4, Accession NM\_003942). Accordingly, utilities of VGAM740 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RPS6KA4. LOC255027 (Accession XM\_170806) is another VGAM740 host target gene. LOC255027 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC255027, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of LOC255027 BINDING SITE, designated SEQ ID:45571, to the nucleotide sequence of VGAM740 RNA, herein designated VGAM RNA, also designated SEQ ID:3451.

[29389] Another function of VGAM740 is therefore inhibition of LOC255027 (Accession XM\_170806). Accordingly, utilities of VGAM740 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255027. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 741 (VGAM741) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29390] VGAM741 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM741 was detected is described hereinabove with reference to Figs. 1–8.

[29391] VGAM741 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Taura Syndrome Virus. VGAM741 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[29392] VGAM741 gene encodes a VGAM741 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM741 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM741 precursor RNA is designated SEQ ID:727, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:727 is located at position 2942 relative to the genome of Taura Syndrome Virus.

[29393] VGAM741 precursor RNA folds onto itself, forming VGAM741 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29394] An enzyme complex designated DICER COMPLEX, `dices` the VGAM741 folded precursor RNA into VGAM741 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM741 RNA is designated SEQ ID:3452, and is provided hereinbelow with reference to the sequence listing part.

[29395] VGAM741 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM741 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM741 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29396] VGAM741 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM741 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM741 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-



quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM741 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM741 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29397] The complementary binding of VGAM741 RNA, herein designated VGAM RNA, to host target binding sites on VGAM741 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM741 host target RNA into VGAM741 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29398] It is appreciated that VGAM741 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM741 host target genes. The mRNA of each one of this plurality of VGAM741 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM741 RNA, herein designated VGAM RNA, and which when bound by VGAM741 RNA causes inhibition of translation of respective one or more VGAM741 host target proteins.

[29399] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM741 gene, herein designated VGAM GENE, on one or more VGAM741 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29400] It is yet further appreciated that a function of VGAM741 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of viral infection by Taura Syndrome Virus. Specific functions, and accordingly utilities, of VGAM741 correlate with, and may be deduced from, the identity of the host target genes which VGAM741 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29401] Nucleotide sequences of the VGAM741 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM741 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM741 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM741 are further described hereinbelow with reference to Table 1.

[29402] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM741 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM741 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29403] As mentioned hereinabove with reference to Fig. 1, a function of VGAM741 gene, herein designated VGAM is inhibition of expression of VGAM741 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM741 correlate with, and may be deduced from, the identity of the target genes which VGAM741 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29404] Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104) is a VGAM741 host target gene. BACE BINDING SITE1 and BACE BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by BACE, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACE BINDING SITE1 and BACE BINDING SITE2, designated SEQ ID:14415 and SEQ ID:29083 respectively, to the nucleotide sequence of

VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29405] A function of VGAM741 is therefore inhibition of Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104), a gene which is responsible for the proteolytic processing of the amyloid precursor protein. Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACE. The function of BACE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM173.Smoothed Homolog (Drosophila) (SMOH, Accession NM\_005631) is another VGAM741 host target gene. SMOH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SMOH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMOH BINDING SITE, designated SEQ ID:12162, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29406] Another function of VGAM741 is therefore inhibition of

Smoothed Homolog (Drosophila) (SMOH, Accession NM\_005631). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMOH. HSA243666 (Accession NM\_017582) is another VGAM741 host target gene. HSA243666 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSA243666, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSA243666 BINDING SITE, designated SEQ ID:19018, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29407] Another function of VGAM741 is therefore inhibition of HSA243666 (Accession NM\_017582). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSA243666. LHPP (Accession NM\_022126) is another VGAM741 host target gene. LHPP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LHPP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LHPP BINDING SITE, designated SEQ ID:22672, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29408] Another function of VGAM741 is therefore inhibition of LHPP (Accession NM\_022126). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LHPP. RIP60 (Accession NM\_013400) is another VGAM741 host target gene. RIP60 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RIP60, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RIP60 BINDING SITE, designated SEQ ID:15058, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29409] Another function of VGAM741 is therefore inhibition of RIP60 (Accession NM\_013400). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RIP60.

LOC123624 (Accession XM\_063761) is another VGAM741 host target gene. LOC123624 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC123624, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC123624 BINDING SITE, designated SEQ ID:37253, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29410] Another function of VGAM741 is therefore inhibition of LOC123624 (Accession XM\_063761). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC123624. LOC131873 (Accession XM\_067585) is another VGAM741 host target gene. LOC131873 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC131873, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC131873 BINDING SITE, designated SEQ ID:37361, to the nucleotide sequence of VGAM741 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3452.

[29411] Another function of VGAM741 is therefore inhibition of LOC131873 (Accession XM\_067585). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC131873. LOC150174 (Accession XM\_086802) is another VGAM741 host target gene. LOC150174 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150174, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150174 BINDING SITE, designated SEQ ID:38869, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29412] Another function of VGAM741 is therefore inhibition of LOC150174 (Accession XM\_086802). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150174. LOC151979 (Accession XM\_087354) is another VGAM741 host target gene. LOC151979 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151979, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151979 BINDING SITE, designated SEQ ID:39189, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29413] Another function of VGAM741 is therefore inhibition of LOC151979 (Accession XM\_087354). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151979. LOC219397 (Accession XM\_167889) is another VGAM741 host target gene. LOC219397 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219397 BINDING SITE, designated SEQ ID:44898, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29414] Another function of VGAM741 is therefore inhibition of LOC219397 (Accession XM\_167889). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC219397. LOC256158 (Accession XM\_175125) is another VGAM741 host target gene. LOC256158 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC256158, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256158 BINDING SITE, designated SEQ ID:46617, to the nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29415] Another function of VGAM741 is therefore inhibition of LOC256158 (Accession XM\_175125). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256158. LOC92223 (Accession XM\_043674) is another VGAM741 host target gene. LOC92223 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC92223, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92223 BINDING SITE, designated SEQ ID:33994, to the

nucleotide sequence of VGAM741 RNA, herein designated VGAM RNA, also designated SEQ ID:3452.

[29416] Another function of VGAM741 is therefore inhibition of LOC92223 (Accession XM\_043674). Accordingly, utilities of VGAM741 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92223. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 742 (VGAM742) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29417] VGAM742 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM742 was detected is described hereinabove with reference to Figs. 1–8.

[29418] VGAM742 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Taura Syndrome Virus. VGAM742 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29419] VGAM742 gene encodes a VGAM742 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM742 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM742 precursor RNA is designated SEQ ID:728, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:728 is located at position 1402 relative to the genome of Taura Syndrome Virus.

[29420] VGAM742 precursor RNA folds onto itself, forming VGAM742 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29421] An enzyme complex designated DICER COMPLEX, `dices` the VGAM742 folded precursor RNA into VGAM742 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM742 RNA is designated SEQ ID:3453, and is provided hereinbelow with reference to the sequence listing part.

[29422] VGAM742 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM742 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM742 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29423] VGAM742 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM742 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM742 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM742 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM742 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29424] The complementary binding of VGAM742 RNA, herein designated VGAM RNA, to host target binding sites on VGAM742 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM742 host target RNA into VGAM742 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29425] It is appreciated that VGAM742 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM742 host target genes. The mRNA of each one of this plurality of VGAM742 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM742 RNA, herein designated VGAM RNA, and which when bound by VGAM742 RNA causes inhibition of translation of respective one or more VGAM742 host target proteins.

[29426] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM742 gene, herein designated VGAM GENE, on one or more VGAM742 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,



`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[29427] It is yet further appreciated that a function of VGAM742 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of viral infection by Taura Syndrome Virus. Specific functions, and accordingly utilities, of VGAM742 correlate with, and may be deduced from, the identity of the host target genes which VGAM742 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29428] Nucleotide sequences of the VGAM742 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM742 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM742 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM742 are further described hereinbelow with reference to Table 1.

[29429] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM742 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM742 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29430] As mentioned hereinabove with reference to Fig. 1, a function of VGAM742 gene, herein designated VGAM is inhibition of expression of VGAM742 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM742 correlate with, and may be deduced from, the identity of the target genes which VGAM742 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29431] BTB and CNC Homology 1, Basic Leucine Zipper Transcription Factor 2 (BACH2, Accession NM\_021813) is a VGAM742 host target gene. BACH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BACH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACH2 BINDING SITE, designated SEQ ID:22377, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29432] A function of VGAM742 is therefore inhibition of BTB and

CNC Homology 1, Basic Leucine Zipper Transcription Factor 2 (BACH2, Accession NM\_021813), a gene which acts as repressor or activator, binds to maf recognition elements. Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACH2. The function of BACH2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM331. Coronin, Actin Binding Protein, 1C (CORO1C, Accession NM\_014325) is another VGAM742 host target gene. CORO1C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CORO1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CORO1C BINDING SITE, designated SEQ ID:15629, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29433] Another function of VGAM742 is therefore inhibition of Coronin, Actin Binding Protein, 1C (CORO1C, Accession NM\_014325). Accordingly, utilities of VGAM742 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with CORO1C. Deoxycytidine Kinase (DCK, Accession NM\_000788) is another VGAM742 host target gene. DCK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DCK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DCK BINDING SITE, designated SEQ ID:6444, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29434] Another function of VGAM742 is therefore inhibition of Deoxycytidine Kinase (DCK, Accession NM\_000788), a gene which mediates the phosphorylation of several deoxyribonucleosides and their analogs. Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DCK. The function of DCK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM538. Secreted Frizzled-related Protein 1 (SFRP1, Accession NM\_003012) is another VGAM742 host target

gene. SFRP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRP1 BINDING SITE, designated SEQ ID:8927, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29435] Another function of VGAM742 is therefore inhibition of Secreted Frizzled-related Protein 1 (SFRP1, Accession NM\_003012), a gene which is a receptor for wnt proteins that may have an anti-apoptotic function. Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRP1. The function of SFRP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM250. Cell Adhesion Molecule with Homology to L1CAM (close homolog of L1) (CHL1, Accession NM\_006614) is another VGAM742 host target gene. CHL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHL1, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHL1 BINDING SITE, designated SEQ ID:13396, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29436] Another function of VGAM742 is therefore inhibition of Cell Adhesion Molecule with Homology to L1CAM (close homolog of L1) (CHL1, Accession NM\_006614). Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHL1. CUB and Sushi Multiple Domains 1 (CSMD1, Accession XM\_054838) is another VGAM742 host target gene. CSMD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSMD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSMD1 BINDING SITE, designated SEQ ID:36185, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29437] Another function of VGAM742 is therefore inhibition of

CUB and Sushi Multiple Domains 1 (CSMD1, Accession XM\_054838). Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSMD1. Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230) is another VGAM742 host target gene. NUDT11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUDT11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUDT11 BINDING SITE, designated SEQ ID:30140, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29438] Another function of VGAM742 is therefore inhibition of Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230). Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUDT11. Phosphodiesterase 10A (PDE10A, Accession NM\_006661) is another VGAM742 host target gene. PDE10A BINDING SITE is HOST TARGET binding site found

in the 3` untranslated region of mRNA encoded by PDE10A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDE10A BINDING SITE, designated SEQ ID:13461, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29439] Another function of VGAM742 is therefore inhibition of Phosphodiesterase 10A (PDE10A, Accession NM\_006661). Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDE10A. RAP140 (Accession NM\_015224) is another VGAM742 host target gene. RAP140 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RAP140, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAP140 BINDING SITE, designated SEQ ID:17553, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29440] Another function of VGAM742 is therefore inhibition of



RAP140 (Accession NM\_015224). Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAP140. LOC146488 (Accession XM\_047748) is another VGAM742 host target gene. LOC146488 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146488, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146488 BINDING SITE, designated SEQ ID:35040, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29441] Another function of VGAM742 is therefore inhibition of LOC146488 (Accession XM\_047748). Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146488. LOC162083 (Accession XM\_091339) is another VGAM742 host target gene. LOC162083 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC162083, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC162083 BINDING SITE, designated SEQ ID:40046, to the nucleotide sequence of VGAM742 RNA, herein designated VGAM RNA, also designated SEQ ID:3453.

[29442] Another function of VGAM742 is therefore inhibition of LOC162083 (Accession XM\_091339). Accordingly, utilities of VGAM742 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162083. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 743 (VGAM743) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29443] VGAM743 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM743 was detected is described hereinabove with reference to Figs. 1–8.

[29444] VGAM743 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Invertebrate Iridescent Virus 6. VGAM743 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in

the human genome.

[29445] VGAM743 gene encodes a VGAM743 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM743 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM743 precursor RNA is designated SEQ ID:729, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:729 is located at position 189563 relative to the genome of Invertebrate Iridescent Virus 6.

[29446] VGAM743 precursor RNA folds onto itself, forming VGAM743 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29447] An enzyme complex designated DICER COMPLEX, `dices` the VGAM743 folded precursor RNA into VGAM743 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM743 RNA is designated SEQ ID:3454, and is provided hereinbelow with reference to the sequence listing part.

[29448] VGAM743 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM743 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM743 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29449] VGAM743 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM743 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM743 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM743 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM743 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29450] The complementary binding of VGAM743 RNA, herein designated VGAM RNA, to host target binding sites on VGAM743 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM743 host target RNA into VGAM743 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29451] It is appreciated that VGAM743 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM743 host target genes. The mRNA of each one of this plurality of VGAM743 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM743 RNA, herein designated VGAM RNA, and which when bound by VGAM743 RNA causes inhibition of translation of respective one or more VGAM743 host target proteins.

[29452] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM743 gene, herein designated VGAM GENE, on one or more VGAM743 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29453] It is yet further appreciated that a function of VGAM743 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of viral infection by Invertebrate Iridescent Virus 6. Specific functions, and accordingly utilities, of VGAM743 correlate with, and may be deduced from, the identity of the host target genes which VGAM743 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29454] Nucleotide sequences of the VGAM743 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM743 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM743 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM743 are further described hereinbelow with reference to Table 1.

[29455] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM743 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM743 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29456] As mentioned hereinabove with reference to Fig. 1, a function of VGAM743 gene, herein designated VGAM is inhibition of expression of VGAM743 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM743 correlate with, and may be deduced from, the identity of the target genes which VGAM743 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29457] COX15 Homolog, Cytochrome C Oxidase Assembly Protein (yeast) (COX15, Accession NM\_078470) is a VGAM743 host target gene. COX15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COX15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COX15 BINDING SITE, designated SEQ ID:27788, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also desig-



nated SEQ ID:3454.

[29458] A function of VGAM743 is therefore inhibition of COX15 Homolog, Cytochrome C Oxidase Assembly Protein (yeast) (COX15, Accession NM\_078470). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COX15. Cysteine and Glycine-rich Protein 1 (CSRP1, Accession NM\_004078) is another VGAM743 host target gene. CSRP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSRP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSRP1 BINDING SITE, designated SEQ ID:10278, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29459] Another function of VGAM743 is therefore inhibition of Cysteine and Glycine-rich Protein 1 (CSRP1, Accession NM\_004078), a gene which could play a role in neuronal development. Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSRP1. The function of CSRP1 has been established by previous studies. The hu-

man gene encoding cysteine-rich protein (CSRP) is a highly conserved, cell cycle-regulated gene that is induced in the immediate early response to serum repletion in serum-starved, noncycling cells. The LIM/double zinc finger motif found in cysteine-rich protein is found in an expanding group of proteins with critical functions in gene regulation, cell growth, and somatic differentiation (Wang et al., 1992). Other members of the group include cysteine-rich intestinal protein (CRIP; 123875), CSRP2 (OMIM Ref. No. 601871), CSRP3 (OMIM Ref. No. 600824), and the rhombotin genes RBTN1 (OMIM Ref. No. 186921), RBTN2 (OMIM Ref. No. 180385), and RBTN3 (OMIM Ref. No. 180386). Weiskirchen et al. (1995) described the CRP family of LIM domain proteins Wang et al. (1992) cloned the human CRP genomic sequence. The CRP gene spans approximately 23.2 kb from the cap site to the polyadenylation site. It contains 6 exons, with a 10.4-kb first intron. The authors showed that CRP is a primary response gene in both human fibroblasts and mouse Balb/c 3T3 cells; in the mouse cells, the kinetic profile of its induction closely paralleled that of c-myc (190080

[29460] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

[29461] Wang, X.; Ray, K.; Szpirer, J.; Levan, G.; Liebhaber, S. A.; Cooke, N. E. : Analysis of the human cysteine-rich protein gene (CSRP), assignment to chromosome 1q24-1q32, and identification of an associated MspI polymorphism. *Genomics* 14: 391-397, 1992. ; and

[29462] Liebhaber, S. A.; Emery, J. G.; Urbanek, M.; Wang, X.; Cooke, N. E. : Characterization of a human cDNA encoding a widely expressed and highly conserved cysteine-rich protein with an unus.

[29463] Further studies establishing the function and utilities of CSRP1 are found in John Hopkins OMIM database record ID 123876, and in cited publications numbered 3977-3979, 3982-398 and 3980 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Exostoses (multiple)-like 2 (EXTL2, Accession NM\_001439) is another VGAM743 host target gene. EXTL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EXTL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EXTL2 BINDING SITE, designated SEQ

ID:7163, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29464] Another function of VGAM743 is therefore inhibition of Exostoses (multiple)-like 2 (EXTL2, Accession NM\_001439), a gene which is homologous to the EXT and EXTL genes. Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EXTL2. The function of EXTL2 has been established by previous studies. In patients with multiple exostoses, mutations in 2 different genes have been found: EXT1 (OMIM Ref. No. 133700) on 8q and EXT2 (OMIM Ref. No. 133701) on 11p. In addition, linkage has demonstrated a third locus, EXT3 (OMIM Ref. No. 600209), on 19p as the site of mutations causing multiple exostoses. The family of EXT genes was extended by the identification of an EXT-like gene (EXTL1; 601738) showing a high degree of homology with the EXT genes. Wuyts et al. (1997) described a second EXT-like gene, EXTL2, that is homologous to the EXT and EXTL genes. EXTL2 was found to consist of 5 exons encoding a ubiquitously expressed 330-amino acid protein. In addition, a putative pseudogene, EXTL2P, was identified. Saito et al. (1998)

also cloned an EXTL2 cDNA, which they called EXTR2. By Northern blot analysis, they detected a 3.4-kb transcript in all tissues tested except leukocyte, where the gene was hardly transcribed. Its expression was relatively constant among tissues, but was weak in liver, lung, and thymus. By fluorescence in situ hybridization, Wuyts et al. (1997) mapped the EXTL2 gene to 1p12-p11 and the EXTL2 pseudogene to 2q24-q31. By somatic cell hybrid and radiation hybrid analyses, Saito et al. (1998) mapped the EXTL2 gene to chromosome 1p21. Wuyts and Van Hul (2000) cloned mouse Extl2, which has the same genomic structure as the human gene, encodes a protein identical in size, and has a sequence that is 87% identical to the human sequence. By radiation hybrid analysis, they mapped the mouse gene to chromosome 3.

[29465] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29466] Wuyts, W.; Van Hul, W.; Hendrickx, J.; Speleman, F.; Wauters, J.; De Boulle, K.; Van Roy, N.; Van Agtmael, T.; Bossuyt, P.; Willems, P. J. : Identification and characterization of a novel member of the EXT gene family, EXTL2. *Eur. J. Hum. Genet.* 5: 382-389, 1997. ; and

[29467] Wuyts, W.; Van Hul, W. : Characterization and genomic localization of the mouse Extl2 gene. Cytogenet. Cell Genet. 89: 185–188, 2000.

[29468] Further studies establishing the function and utilities of EXTL2 are found in John Hopkins OMIM database record ID 602411, and in cited publications numbered 6016–6018 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Sparc/osteonectin, Cwcv and Kazal-like Domains Proteoglycan (testican) (SPOCK, Accession XM\_031696) is another VGAM743 host target gene. SPOCK BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SPOCK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPOCK BINDING SITE, designated SEQ ID:31457, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29469] Another function of VGAM743 is therefore inhibition of Sparc/osteonectin, Cwcv and Kazal-like Domains Proteoglycan (testican) (SPOCK, Accession XM\_031696). Accordingly, utilities of VGAM743 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with SPOCK. Bromodomain Containing 2 (BRD2, Accession NM\_005104) is another VGAM743 host target gene. BRD2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BRD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BRD2 BINDING SITE, designated SEQ ID:11575, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29470] Another function of VGAM743 is therefore inhibition of Bromodomain Containing 2 (BRD2, Accession NM\_005104). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BRD2. FLJ12747 (Accession NM\_032173) is another VGAM743 host target gene. FLJ12747 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12747, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12747 BINDING SITE, designated SEQ

ID:25880, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29471] Another function of VGAM743 is therefore inhibition of FLJ12747 (Accession NM\_032173). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12747. Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445) is another VGAM743 host target gene. GRIN3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRIN3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRIN3A BINDING SITE, designated SEQ ID:28540, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29472] Another function of VGAM743 is therefore inhibition of Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRIN3A.



HSPC054 (Accession NM\_014152) is another VGAM743 host target gene. HSPC054 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPC054, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC054 BINDING SITE, designated SEQ ID:15434, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29473] Another function of VGAM743 is therefore inhibition of HSPC054 (Accession NM\_014152). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC054. KIAA0016 (Accession NM\_014765) is another VGAM743 host target gene. KIAA0016 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0016, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0016 BINDING SITE, designated SEQ ID:16534, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3454.

[29474] Another function of VGAM743 is therefore inhibition of KIAA0016 (Accession NM\_014765). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0016. P311 (Accession NM\_004772) is another VGAM743 host target gene. P311 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P311, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P311 BINDING SITE, designated SEQ ID:11163, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29475] Another function of VGAM743 is therefore inhibition of P311 (Accession NM\_004772). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P311. PA26 (Accession NM\_014454) is another VGAM743 host target gene. PA26 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PA26, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PA26 BINDING SITE, designated SEQ ID:15807, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29476] Another function of VGAM743 is therefore inhibition of PA26 (Accession NM\_014454). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PA26. Sideroflexin 5 (SFXN5, Accession NM\_144579) is another VGAM743 host target gene. SFXN5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFXN5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFXN5 BINDING SITE, designated SEQ ID:29386, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29477] Another function of VGAM743 is therefore inhibition of Sideroflexin 5 (SFXN5, Accession NM\_144579). Accordingly, utilities of VGAM743 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with SFXN5. LOC196027 (Accession XM\_113633) is another VGAM743 host target gene. LOC196027 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC196027, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196027 BINDING SITE, designated SEQ ID:42305, to the nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29478] Another function of VGAM743 is therefore inhibition of LOC196027 (Accession XM\_113633). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196027. LOC81034 (Accession NM\_030780) is another VGAM743 host target gene. LOC81034 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC81034, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC81034 BINDING SITE, designated SEQ ID:25070, to the

nucleotide sequence of VGAM743 RNA, herein designated VGAM RNA, also designated SEQ ID:3454.

[29479] Another function of VGAM743 is therefore inhibition of LOC81034 (Accession NM\_030780). Accordingly, utilities of VGAM743 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC81034. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 744 (VGAM744) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29480] VGAM744 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM744 was detected is described hereinabove with reference to Figs. 1–8.

[29481] VGAM744 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM744 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29482] VGAM744 gene encodes a VGAM744 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM744 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM744 precursor RNA is designated SEQ ID:730, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:730 is located at position 1346 relative to the genome of Bovine Coronavirus.

[29483] VGAM744 precursor RNA folds onto itself, forming VGAM744 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29484] An enzyme complex designated DICER COMPLEX, `dices` the VGAM744 folded precursor RNA into VGAM744 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM744 RNA is designated SEQ ID:3455, and is provided hereinbelow with reference to the sequence listing part.

[29485] VGAM744 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM744 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM744 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[29486] VGAM744 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM744 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM744 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM744 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM744 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29487] The complementary binding of VGAM744 RNA, herein designated VGAM RNA, to host target binding sites on VGAM744 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM744 host target RNA into VGAM744 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29488] It is appreciated that VGAM744 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents



a plurality of VGAM744 host target genes. The mRNA of each one of this plurality of VGAM744 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM744 RNA, herein designated VGAM RNA, and which when bound by VGAM744 RNA causes inhibition of translation of respective one or more VGAM744 host target proteins.

[29489] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM744 gene, herein designated VGAM GENE, on one or more VGAM744 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[29490] It is yet further appreciated that a function of VGAM744 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM744 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM744 correlate with, and may be deduced from, the identity of the host target genes which VGAM744 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[29491] Nucleotide sequences of the VGAM744 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM744 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM744 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM744 are further described hereinbelow with reference to Table 1.

[29492] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM744 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM744 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29493] As mentioned hereinabove with reference to Fig. 1, a function of VGAM744 gene, herein designated VGAM is inhibition of expression of VGAM744 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM744 correlate with, and may be deduced from, the identity of the target genes which VGAM744 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29494] Tropomyosin 4 (TPM4, Accession NM\_003290) is a VGAM744 host target gene. TPM4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TPM4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TPM4 BINDING SITE, designated SEQ ID:9299, to the nucleotide sequence of VGAM744 RNA, herein designated VGAM RNA, also designated SEQ ID:3455.

[29495] A function of VGAM744 is therefore inhibition of Tropomyosin 4 (TPM4, Accession NM\_003290), a gene

which plays a central role, in association with the troponin complex, in the calcium dependent regulation of vertebrate striated muscle contraction. Accordingly, utilities of VGAM744 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TPM4. The function of TPM4 has been established by previous studies. Vertebrates have at least 4 different tropomyosin genes; in humans, they are named TPM1 (OMIM Ref. No. 191010), TPM2 (OMIM Ref. No. 190990), TPM3 (OMIM Ref. No. 191030), and TPM4. Both the muscle and nonmuscle isoforms of the tropomyosins are expressed through alternative splicing of each of the 4 genes. Laing et al. (1995) referred to unpublished observations indicating that the TPM4 gene maps to human chromosome 19. Wilton et al. (1996) developed sequence tagged sites (STS) for the TPM4 gene. One STS was used to amplify DNA from somatic cell hybrids to localize TPM4 to chromosome 19. The other, a product from a long-range PCR, was used directly as a probe to refine the localization of TPM4 to 19p13.1 by fluorescence in situ hybridization to metaphase chromosome spreads.

[29496] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [29497] Laing, N. G.; Wilton, S. D.; Akkari, P. A.; Dorosz, S.; Boundy, K.; Kneebone, C.; Blumbergs, P.; White, S.; Watkins, H.; Love, D. R.; Haan, E. : A mutation in the alpha tropomyosin gene TPM3 associated with autosomal dominant nemaline myopathy. *Nature Genet.* 9: 75–79, 1995. ; and
- [29498] Wilton, S. D.; Lim, L.; Dorosz, S. D.; Gunn, H. C.; Eyre, H. J.; Callen, D. F.; Laing, N. G. : Assignment of the human alpha-tropomyosin gene TPM4 to band 19p13.1 by fluorescence in situ hy.
- [29499] Further studies establishing the function and utilities of TPM4 are found in John Hopkins OMIM database record ID 600317, and in cited publications numbered 300 and 7225 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger Protein 135 (clone pHZ-17) (ZNF135, Accession NM\_003436) is another VGAM744 host target gene. ZNF135 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZNF135, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

ZNF135 BINDING SITE, designated SEQ ID:9488, to the nucleotide sequence of VGAM744 RNA, herein designated VGAM RNA, also designated SEQ ID:3455.

[29500] Another function of VGAM744 is therefore inhibition of Zinc Finger Protein 135 (clone pHZ-17) (ZNF135, Accession NM\_003436). Accordingly, utilities of VGAM744 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF135. DKFZp434C0923 (Accession NM\_017598) is another VGAM744 host target gene. DKFZp434C0923 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp434C0923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434C0923 BINDING SITE, designated SEQ ID:19060, to the nucleotide sequence of VGAM744 RNA, herein designated VGAM RNA, also designated SEQ ID:3455.

[29501] Another function of VGAM744 is therefore inhibition of DKFZp434C0923 (Accession NM\_017598). Accordingly, utilities of VGAM744 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with DKFZp434C0923. DKFZp566H0824 (Accession NM\_017535) is another VGAM744 host target gene. DKFZp566H0824 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp566H0824, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp566H0824 BINDING SITE, designated SEQ ID:18972, to the nucleotide sequence of VGAM744 RNA, herein designated VGAM RNA, also designated SEQ ID:3455.

[29502] Another function of VGAM744 is therefore inhibition of DKFZp566H0824 (Accession NM\_017535). Accordingly, utilities of VGAM744 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp566H0824. LOC152106 (Accession XM\_046399) is another VGAM744 host target gene. LOC152106 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152106 BINDING SITE, desig-

nated SEQ ID:34708, to the nucleotide sequence of VGAM744 RNA, herein designated VGAM RNA, also designated SEQ ID:3455.

[29503] Another function of VGAM744 is therefore inhibition of LOC152106 (Accession XM\_046399). Accordingly, utilities of VGAM744 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152106. LOC255152 (Accession XM\_173310) is another VGAM744 host target gene. LOC255152 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255152, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255152 BINDING SITE, designated SEQ ID:46533, to the nucleotide sequence of VGAM744 RNA, herein designated VGAM RNA, also designated SEQ ID:3455.

[29504] Another function of VGAM744 is therefore inhibition of LOC255152 (Accession XM\_173310). Accordingly, utilities of VGAM744 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255152. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the



present invention, referred to here as Viral Genomic Address Messenger 745 (VGAM745) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29505] VGAM745 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM745 was detected is described hereinabove with reference to Figs. 1–8.

[29506] VGAM745 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM745 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29507] VGAM745 gene encodes a VGAM745 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM745 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM745 precursor RNA is designated SEQ ID:731, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:731 is located at position 18815 relative to the genome of

## Bovine Coronavirus.

[29508] VGAM745 precursor RNA folds onto itself, forming VGAM745 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29509] An enzyme complex designated DICER COMPLEX, `dices` the VGAM745 folded precursor RNA into VGAM745 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 48%) nucleotide sequence of VGAM745 RNA is designated SEQ ID:3456, and is provided hereinbelow with reference to the sequence listing part.

[29510] VGAM745 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM745 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM745 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29511] VGAM745 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM745 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM745 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM745 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM745 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29512] The complementary binding of VGAM745 RNA, herein designated VGAM RNA, to host target binding sites on VGAM745 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM745 host target RNA into VGAM745 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29513] It is appreciated that VGAM745 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM745 host target genes. The mRNA of each one of this plurality of VGAM745 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM745 RNA, herein designated VGAM RNA, and which when bound by VGAM745 RNA causes inhibition of translation of respective one or more VGAM745 host target proteins.

[29514] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM745 gene, herein designated VGAM GENE, on one or more VGAM745 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29515] It is yet further appreciated that a function of VGAM745 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM745 correlate

with, and may be deduced from, the identity of the host target genes which VGAM745 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29516] Nucleotide sequences of the VGAM745 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM745 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM745 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM745 are further described hereinbelow with reference to Table 1.

[29517] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM745 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM745 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29518] As mentioned hereinabove with reference to Fig. 1, a function of VGAM745 gene, herein designated VGAM is inhibition of expression of VGAM745 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM745 correlate with, and may be deduced

from, the identity of the target genes which VGAM745 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29519] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_019900) is a VGAM745 host target gene. ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABCC1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3, designated SEQ ID:21283, SEQ ID:21287 and SEQ ID:11439 respectively, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29520] A function of VGAM745 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_019900), a gene which may participate directly in the active transport of drugs into sub-cellular organelles or influence drug distribution indirectly. Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical con-

ditions associated with ABCC1. The function of ABCC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM479. Chloride Intracellular Channel 4 (CLIC4, Accession NM\_013943) is another VGAM745 host target gene. CLIC4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLIC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLIC4 BINDING SITE, designated SEQ ID:15131, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29521] Another function of VGAM745 is therefore inhibition of Chloride Intracellular Channel 4 (CLIC4, Accession NM\_013943). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLIC4. FLJ13194 (Accession NM\_025146) is another VGAM745 host target gene. FLJ13194 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13194, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13194 BINDING SITE, designated SEQ ID:24786, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29522] Another function of VGAM745 is therefore inhibition of FLJ13194 (Accession NM\_025146). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13194. KIAA1753 (Accession XM\_036115) is another VGAM745 host target gene. KIAA1753 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1753, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1753 BINDING SITE, designated SEQ ID:32383, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29523] Another function of VGAM745 is therefore inhibition of KIAA1753 (Accession XM\_036115). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1753. Kelch-like 4 (Drosophila) (KLHL4, Accession NM\_019117) is another VGAM745 host target gene. KLHL4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KLHL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KLHL4 BINDING SITE, designated SEQ ID:21196, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29524] Another function of VGAM745 is therefore inhibition of Kelch-like 4 (Drosophila) (KLHL4, Accession NM\_019117). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KLHL4. LOC200609 (Accession XM\_117256) is another VGAM745 host target gene. LOC200609 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200609, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of LOC200609 BINDING SITE, designated SEQ ID:43330, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29525] Another function of VGAM745 is therefore inhibition of LOC200609 (Accession XM\_117256). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200609. LOC220980 (Accession XM\_167629) is another VGAM745 host target gene. LOC220980 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220980, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220980 BINDING SITE, designated SEQ ID:44739, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29526] Another function of VGAM745 is therefore inhibition of LOC220980 (Accession XM\_167629). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220980. LOC254556 (Accession XM\_170588) is an-

other VGAM745 host target gene. LOC254556 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254556 BINDING SITE, designated SEQ ID:45394, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29527] Another function of VGAM745 is therefore inhibition of LOC254556 (Accession XM\_170588). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254556. LOC93538 (Accession XM\_051927) is another VGAM745 host target gene. LOC93538 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93538 BINDING SITE, designated SEQ ID:35922, to the nucleotide sequence of VGAM745 RNA, herein designated VGAM RNA, also designated SEQ ID:3456.

[29528] Another function of VGAM745 is therefore inhibition of LOC93538 (Accession XM\_051927). Accordingly, utilities of VGAM745 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93538. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 746 (VGAM746) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29529] VGAM746 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM746 was detected is described hereinabove with reference to Figs. 1–8.

[29530] VGAM746 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM746 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29531] VGAM746 gene encodes a VGAM746 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM746

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM746 precursor RNA is designated SEQ ID:732, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:732 is located at position 13256 relative to the genome of Bovine Coronavirus.

[29532] VGAM746 precursor RNA folds onto itself, forming VGAM746 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29533] An enzyme complex designated DICER COMPLEX, `dices` the VGAM746 folded precursor RNA into VGAM746 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 45%) nucleotide sequence of VGAM746 RNA is designated SEQ ID:3457, and is provided hereinbelow with reference to the sequence listing part.

[29534] VGAM746 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM746 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM746 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[29535] VGAM746 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM746 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM746 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM746 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM746 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29536] The complementary binding of VGAM746 RNA, herein designated VGAM RNA, to host target binding sites on VGAM746 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM746 host target RNA into VGAM746 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29537] It is appreciated that VGAM746 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM746 host target genes. The mRNA of each one of this plurality of VGAM746 host target genes



comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM746 RNA, herein designated VGAM RNA, and which when bound by VGAM746 RNA causes inhibition of translation of respective one or more VGAM746 host target proteins.

[29538] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM746 gene, herein designated VGAM GENE, on one or more VGAM746 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29539] It is yet further appreciated that a function of VGAM746 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM746 correlate with, and may be deduced from, the identity of the host target genes which VGAM746 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29540] Nucleotide sequences of the VGAM746 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM746 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM746 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM746 are further described hereinbelow with reference to Table 1.

[29541] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM746 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM746 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[29542] As mentioned hereinabove with reference to Fig. 1, a function of VGAM746 gene, herein designated VGAM is inhibition of expression of VGAM746 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM746 correlate with, and may be deduced from, the identity of the target genes which VGAM746 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29543] Glutamate Receptor, Metabotropic 7 (GRM7, Accession NM\_000844) is a VGAM746 host target gene. GRM7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRM7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRM7 BINDING SITE, designated SEQ ID:6518, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29544] A function of VGAM746 is therefore inhibition of Glutamate Receptor, Metabotropic 7 (GRM7, Accession NM\_000844), a gene which is mediated by a g-protein that inhibits adenylate cyclase activity. Accordingly, utili-

ties of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRM7. The function of GRM7 has been established by previous studies. L-glutamate, a major excitatory neurotransmitter, interacts with both ionotropic and metabotropic glutamate receptors. See mGluR3 (OMIM Ref. No. 601115). The metabotropic glutamate receptors (OMIM Ref. No. mGluRs), which are G protein-coupled receptors, have been divided into 3 groups on the basis of sequence homology, putative signal transduction mechanisms, and pharmacologic properties. Group II and group III mGluRs are linked to the inhibition of the cyclic AMP cascade, but differ in their agonist selectivities. Okamoto et al. (1994) isolated cDNAs encoding rat mGluR7. The predicted mGluR7 protein shares the structural profile of other mGluRs, with a signal peptide and a large extracellular domain followed by 7 membrane-spanning domains. This receptor shows a high degree of similarity to the group III receptors mGluR4 (OMIM Ref. No. 604100) and mGluR6 (OMIM Ref. No. 604096) in terms of both amino acid sequence and agonist selectivity. In situ hybridization to rat brain tissues indicated that the mGluR7 gene is expressed widely, unlike mGluR4 and mGluR6. Wu et al.

(1998) and Makoff et al. (1996) isolated human brain cDNAs encoding mGluR7. They both reported that the predicted 915-amino acid human protein is 99% identical to rat mGluR7. Wu et al. (1998) stated that the group III human receptors, mGluR7, mGluR4, and mGluR8 (OMIM Ref. No. 601116), share 67 to 70% protein sequence similarity with each other and 42 to 45% similarity with the group I and group II receptors. Using in situ hybridization, Makoff et al. (1996) determined that mGluR7 is expressed in many areas of the human brain, especially in the cerebral cortex, hippocampus, and cerebellum.

[29545] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29546] Okamoto, N.; Hori, S.; Akazawa, C.; Hayashi, Y.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. : Molecular characterization of a new metabotropic glutamate receptor mGluR7 coupled to inhibitory cyclic AMP signal transduction. J. Biol. Chem. 269: 1231-1236, 1994. ; and

[29547] Wu, S.; Wright, R. A.; Rockey, P. K.; Burgett, S. G.; Arnold, J. S.; Rosteck, P. R., Jr.; Johnson, B. G.; Schoepp, D. D.; Belagaje, R. M. : Group III human metabotropic glutamate recept.

[29548] Further studies establishing the function and utilities of GRM7 are found in John Hopkins OMIM database record ID 604101, and in cited publications numbered 504 and 7055 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Mannosyl (alpha-1,6-)-glycoprotein Beta-1,6-N-acetyl-glucosaminyltransferase (MGAT5, Accession NM\_002410) is another VGAM746 host target gene. MGAT5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGAT5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAT5 BINDING SITE, designated SEQ ID:8240, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29549] Another function of VGAM746 is therefore inhibition of Mannosyl (alpha-1,6-)-glycoprotein Beta-1,6-N-acetyl-glucosaminyltransferase (MGAT5, Accession NM\_002410). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGAT5. X-box Binding Pro-

tein 1 (XBP1, Accession NM\_005080) is another VGAM746 host target gene. XBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XBP1 BINDING SITE, designated SEQ ID:11533, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29550] Another function of VGAM746 is therefore inhibition of X-box Binding Protein 1 (XBP1, Accession NM\_005080), a gene which has a role in transcriptional regulation. Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XBP1. The function of XBP1 has been established by previous studies. The class II major histocompatibility complex antigens are a family of integral membrane proteins whose expression is tissue-specific and developmentally regulated. Three consensus sequences, X1, X2, and Y, separated by an interspace element, are found upstream from all class II genes. Deletion of each of these sequences eliminates expression of class II genes in

vitro and in transgenic mice. Liou et al. (1990) isolated a cDNA encoding a DNA-binding protein whose target is the X boxes of DR-alpha and DP-beta. Liou et al. (1991) found that the protein, which they referred to as XBP1, acts as a transcription factor in B cells by recognizing both the X2 promoter element of both the human DR-alpha and DP-beta and mouse A-alpha genes. The cDNA for the XBP1 gene hybridized to human RNA species of approximately 2.2 kb and 2.6 kb, which were expressed in class II negative as well as class II positive cells. By in situ hybridization analysis, Reimold et al. (2001) demonstrated that XBP1 was expressed at high levels in plasma cells in rheumatoid synovium from 2 patients. By analysis of interspecies somatic cell hybrids, Liou et al. (1991) demonstrated that the XBP1 gene is located in the region 22pter-q13. A pseudogene was shown to be located on chromosome 5. Calfon et al. (2002) showed that the unfolded protein response (UPR) requires intact Ire1 (OMIM Ref. No. 604033) and Xbp1 in *C. elegans*. Both mouse and worm Ire1 splice a small intron from Xbp1 mRNA in response to UPR activation. Immunoblot analysis showed that, in the mouse, the processed, but not the unprocessed, 54-kD Xbp1 protein accumulates during the UPR



and depends on Ire1. Calton et al. (2002) proposed that an increased load of proteins in the endoplasmic reticulum activates Xbp1 and triggers the development of an elaborate secretory process, as seen in plasma cells. Animal model experiments lend further support to the function of XBP1. By injecting Xbp1-deficient embryonic stem cells into Rag2 (OMIM Ref. No. 179616)-deficient blastocysts, Reimold et al. (2001) generated viable Xbp1  $-/-$  mice. In these chimeric animals, Xbp1-deficient cells were abundant in lymphoid organs, variably expressed in other organs, and nearly absent from liver, consistent with the essential role of XBP1 in hepatocyte development. ELISA analysis showed low levels of immunoglobulin produced by Xbp1  $-/-$  B cells, which could be reversed by transduction of Xbp1 into the B cells. Phenotype analysis indicated that Xbp1-deficient B and T cells could be activated to undergo proliferation, cell-surface activation-marker expression, class switch recombination, and cytokine secretion at normal levels. Histologic analysis revealed a dearth of plasma cells in the organs of Xbp1  $-/-$  mice, and the cells did not express syndecan-1 (SDC1; 186355), a marker for terminally differentiated plasma cells, after immunization with DNP-albumin. Although B cells were gen-

erated in normal numbers and germinal center formation was normal, Xbp1  $-/-$  mice did not make serum antibody in response to either T cell-dependent or -independent antigens or to polyoma virus, which is normally controlled by antibodies alone. Reimold et al. (2001) concluded that the defect in Xbp1-deficient mice is distal to the effects of transcription factors essential for germinal-center formation, such as Bcl3 (OMIM Ref. No. 109560), Bcl6 (OMIM Ref. No. 109565), Nfkb (OMIM Ref. No. 164011), and Irf4 (OMIM Ref. No. 601900), and distal to the expression of Irf4 and Blimp1 (PRDM1; 603423) in immature plasma cells exiting from germinal centers. They proposed that XBP1 has target genes that are essential in plasma-cell generation

[29551] It is appreciated that the abovementioned animal model for XBP1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[29552] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29553] Calfon, M.; Zeng, H.; Urano, F.; Till, J. H.; Hubbard, S. R.; Harding, H. P.; Clark, S. G.; Ron, D. : IRE1 couples endo-

plasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. Nature 415: 92-96, 2002. ; and

[29554] Reimold, A. M.; Iwakoshi, N. N.; Manis, J.; Vallabhajosyula, P.; Szomolanyi-Tsuda, E.; Gravallesse, E. M.; Friend, D.; Grusby, M. J.; Alt, F.; Glimcher, L. H. : Plasma cell differentiation.

[29555] Further studies establishing the function and utilities of XBP1 are found in John Hopkins OMIM database record ID 194355, and in cited publications numbered 6040-6043 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZP434B044 (Accession NM\_031476) is another VGAM746 host target gene. DKFZP434B044 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434B044, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434B044 BINDING SITE, designated SEQ ID:25553, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29556] Another function of VGAM746 is therefore inhibition of DKFZP434B044 (Accession NM\_031476). Accordingly,

utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434B044. FLJ12806 (Accession NM\_022831) is another VGAM746 host target gene. FLJ12806 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12806, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12806 BINDING SITE, designated SEQ ID:23112, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29557] Another function of VGAM746 is therefore inhibition of FLJ12806 (Accession NM\_022831). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12806. FLJ22635 (Accession NM\_025092) is another VGAM746 host target gene. FLJ22635 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22635, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22635 BINDING SITE,

designated SEQ ID:24716, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29558] Another function of VGAM746 is therefore inhibition of FLJ22635 (Accession NM\_025092). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22635. FLJ23604 (Accession NM\_025064) is another VGAM746 host target gene. FLJ23604 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23604, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23604 BINDING SITE, designated SEQ ID:24661, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29559] Another function of VGAM746 is therefore inhibition of FLJ23604 (Accession NM\_025064). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23604. KIAA0557 (Accession XM\_085507) is another VGAM746 host target gene. KIAA0557 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by KIAA0557, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0557 BINDING SITE, designated SEQ ID:38202, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29560] Another function of VGAM746 is therefore inhibition of KIAA0557 (Accession XM\_085507). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0557. LOC144742 (Accession XM\_084949) is another VGAM746 host target gene. LOC144742 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144742, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144742 BINDING SITE, designated SEQ ID:37777, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29561] Another function of VGAM746 is therefore inhibition of

LOC144742 (Accession XM\_084949). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144742. LOC145842 (Accession XM\_085254) is another VGAM746 host target gene. LOC145842 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145842, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145842 BINDING SITE, designated SEQ ID:37997, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29562] Another function of VGAM746 is therefore inhibition of LOC145842 (Accession XM\_085254). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145842. LOC153711 (Accession XM\_098419) is another VGAM746 host target gene. LOC153711 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153711, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC153711 BINDING SITE, designated SEQ ID:41668, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29563] Another function of VGAM746 is therefore inhibition of LOC153711 (Accession XM\_098419). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153711. LOC51008 (Accession NM\_015947) is another VGAM746 host target gene. LOC51008 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51008, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51008 BINDING SITE, designated SEQ ID:18064, to the nucleotide sequence of VGAM746 RNA, herein designated VGAM RNA, also designated SEQ ID:3457.

[29564] Another function of VGAM746 is therefore inhibition of LOC51008 (Accession NM\_015947). Accordingly, utilities of VGAM746 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51008. Fig. 1 further provides a conceptual descrip-



tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 747 (VGAM747) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29565] VGAM747 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM747 was detected is described hereinabove with reference to Figs. 1–8.

[29566] VGAM747 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM747 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29567] VGAM747 gene encodes a VGAM747 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM747 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM747 precursor RNA is designated SEQ ID:733, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:733 is located at position 1579 relative to the genome of Bovine Coronavirus.

[29568] VGAM747 precursor RNA folds onto itself, forming VGAM747 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29569] An enzyme complex designated DICER COMPLEX, `dices` the VGAM747 folded precursor RNA into VGAM747 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM747 RNA is designated SEQ ID:3458, and is provided hereinbelow with reference to the sequence listing part.

[29570] VGAM747 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM747 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM747 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29571] VGAM747 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM747 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM747 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM747 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM747 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[29572] The complementary binding of VGAM747 RNA, herein designated VGAM RNA, to host target binding sites on VGAM747 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM747 host target RNA into VGAM747 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29573] It is appreciated that VGAM747 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM747 host target genes. The mRNA of each one of this plurality of VGAM747 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM747 RNA, herein designated VGAM RNA, and which when bound by VGAM747 RNA causes inhibition of translation of respective one or more VGAM747 host target proteins.

[29574] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM747 gene, herein designated VGAM GENE, on one or more VGAM747 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[29575] It is yet further appreciated that a function of VGAM747 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM747 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM747 correlate with, and may be deduced from, the identity of the host target genes which VGAM747 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29576] Nucleotide sequences of the VGAM747 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM747 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM747 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM747 are further described hereinbelow with reference to Table 1.

[29577] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM747 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM747 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29578] As mentioned hereinabove with reference to Fig. 1, a function of VGAM747 gene, herein designated VGAM is inhibition of expression of VGAM747 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM747 correlate with, and may be deduced from, the identity of the target genes which VGAM747 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29579] Discs, Large (Drosophila) Homolog 5 (DLG5, Accession XM\_096398) is a VGAM747 host target gene. DLG5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DLG5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLG5 BINDING SITE, designated SEQ ID:40331, to the nucleotide sequence of VGAM747 RNA, herein designated VGAM RNA, also designated SEQ ID:3458.

[29580] A function of VGAM747 is therefore inhibition of Discs,

Large (Drosophila) Homolog 5 (DLG5, Accession XM\_096398), a gene which may transmit extracellular signals to inhibit cell proliferation. Accordingly, utilities of VGAM747 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLG5. The function of DLG5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM444.FBJ Murine Osteosarcoma Viral Oncogene Homolog B (FOSB, Accession NM\_006732) is another VGAM747 host target gene. FOSB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FOSB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOSB BINDING SITE, designated SEQ ID:13580, to the nucleotide sequence of VGAM747 RNA, herein designated VGAM RNA, also designated SEQ ID:3458.

[29581] Another function of VGAM747 is therefore inhibition of FBJ Murine Osteosarcoma Viral Oncogene Homolog B (FOSB, Accession NM\_006732), a gene which interacts with jun proteins enhancing their dna binding activity. Ac-



cordingly, utilities of VGAM747 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOSB. The function of FOSB has been established by previous studies. Cocaine enhances dopamine-mediated neurotransmission by blocking dopamine reuptake at axon terminals. Most dopamine-containing nerve terminals innervate medium spiny neurons in the striatum of the brain. Cocaine addiction is thought to stem, in part, from neural adaptations that act to maintain equilibrium by countering the effects of repeated drug administration. Chronic exposure to cocaine upregulates several transcription factors that alter gene expression and which could mediate such compensatory neural and behavioral changes. One such transcription factor is delta-FosB, a protein that persists in striatum long after the end of cocaine exposure. Using DNA array analysis of striatal material from inducible transgenic mice, Bibb et al. (2001) identified Cdk5 (OMIM Ref. No. 123831) as a downstream target of delta-FosB. Overexpression of delta-FosB, or chronic cocaine administration, raised levels of Cdk5 mRNA, protein, and activity in the striatum. Moreover, injection of Cdk5 inhibitors into the striatum potentiated behavioral effects of repeated cocaine administration.

Bibb et al. (2001) concluded that changes in Cdk5 levels mediated by delta-FosB, and resulting alterations in signaling involving D1 dopamine receptors, contribute to adaptive changes in the brain related to cocaine addiction. Animal model experiments lend further support to the function of FOSB. Brown et al. (1996) demonstrated that mice in whom the FOSB gene had been inactivated by homologous recombination displayed a profound defect in reproduction. The reproductive failure of fosB mutant mice was due to a specific behavioral defect that resulted in an inability to nurture young. This nurturing defect was seen not only in postpartum females but also in young females and males. Together, these findings provided evidence that nurturing behavior in mammals is genetically controlled and that an immediate early gene, FOSB, is critical for an adaptive neuronal response. Brown et al. (1996) speculated that the nurturing defect is likely due to the absence of FOSB in the preoptic area, a region of the hypothalamus that is critical for nurturing. They stated that this is an example of a transcription factor that controls a complex behavior by regulating a specific neuronal circuit.

[29582] It is appreciated that the abovementioned animal model for FOSB is acknowledged by those skilled in the art as a

scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[29583] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29584] Bibb, J. A.; Chen, J.; Taylor, J. R.; Svenningsson, P.; Nishi, A.; Snyder, G. L.; Yan, Z.; Sagawa, Z. K.; Ouimet, C. C.; Nairn, A. C.; Nestler, E. J.; Greengard, P. : Effects of chronic exposure to cocaine are regulated by the neuronal protein Cdk5. *Nature* 410: 376–380, 2001. ; and

[29585] Brown, J. R.; Ye, H.; Bronson, R. T.; Dikkes, P.; Greenberg, M. E. : A defect in nurturing in mice lacking the immediate early gene *fosB*. *Cell* 86: 297–309, 1996.

[29586] Further studies establishing the function and utilities of FOSB are found in John Hopkins OMIM database record ID 164772, and in cited publications numbered 4341–3828, 383 and 3830–3831 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LOC130813 (Accession XM\_065904) is another VGAM747 host target gene. LOC130813 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130813, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130813 BINDING SITE, designated SEQ ID:37305, to the nucleotide sequence of VGAM747 RNA, herein designated VGAM RNA, also designated SEQ ID:3458.

[29587] Another function of VGAM747 is therefore inhibition of LOC130813 (Accession XM\_065904). Accordingly, utilities of VGAM747 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130813. LOC202460 (Accession XM\_114493) is another VGAM747 host target gene. LOC202460 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202460, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202460 BINDING SITE, designated SEQ ID:42979, to the nucleotide sequence of VGAM747 RNA, herein designated VGAM RNA, also designated SEQ ID:3458.

[29588] Another function of VGAM747 is therefore inhibition of LOC202460 (Accession XM\_114493). Accordingly, utilities of VGAM747 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC202460. LOC221895 (Accession XM\_166511) is another VGAM747 host target gene. LOC221895 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221895 BINDING SITE, designated SEQ ID:44441, to the nucleotide sequence of VGAM747 RNA, herein designated VGAM RNA, also designated SEQ ID:3458.

[29589] Another function of VGAM747 is therefore inhibition of LOC221895 (Accession XM\_166511). Accordingly, utilities of VGAM747 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221895. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 748 (VGAM748) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29590] VGAM748 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM748 was detected is described hereinabove with reference to Figs. 1–8.

[29591] VGAM748 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus.

VGAM748 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29592] VGAM748 gene encodes a VGAM748 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM748 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM748 precursor RNA is designated SEQ ID:734, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:734 is located at position 20531 relative to the genome of Bovine Coronavirus.

[29593] VGAM748 precursor RNA folds onto itself, forming VGAM748 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29594] An enzyme complex designated DICER COMPLEX, `dices` the VGAM748 folded precursor RNA into VGAM748 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM748 RNA is designated SEQ ID:3459, and is provided hereinbelow with reference to the sequence listing part.

[29595] VGAM748 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM748 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM748 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29596] VGAM748 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM748 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM748 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM748 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM748 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[29597] The complementary binding of VGAM748 RNA, herein designated VGAM RNA, to host target binding sites on



VGAM748 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM748 host target RNA into VGAM748 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29598] It is appreciated that VGAM748 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM748 host target genes. The mRNA of each one of this plurality of VGAM748 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM748 RNA, herein designated VGAM RNA, and which when bound by VGAM748 RNA causes inhibition of translation of respective one or more VGAM748 host target proteins.

[29599] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM748 gene, herein designated VGAM GENE, on one or more VGAM748 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29600] It is yet further appreciated that a function of VGAM748 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM748 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM748 correlate with, and may be deduced from, the identity of the host target genes which VGAM748 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29601] Nucleotide sequences of the VGAM748 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM748 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM748 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM748 are further described hereinbelow with reference to Table 1.

[29602] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM748 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM748 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29603] As mentioned hereinabove with reference to Fig. 1, a function of VGAM748 gene, herein designated VGAM is inhibition of expression of VGAM748 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM748 correlate with, and may be deduced from, the identity of the target genes which VGAM748 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29604] FLJ11280 (Accession NM\_018379) is a VGAM748 host target gene. FLJ11280 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ11280, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11280 BINDING SITE, designated SEQ ID:20405, to the nucleotide sequence of VGAM748 RNA, herein designated VGAM RNA, also designated SEQ ID:3459.

[29605] A function of VGAM748 is therefore inhibition of FLJ11280 (Accession NM\_018379). Accordingly, utilities of VGAM748 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11280. KIAA0172 (Accession XM\_036295) is another VGAM748 host target gene. KIAA0172 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0172, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0172 BINDING SITE, designated SEQ ID:32410, to the nucleotide sequence of VGAM748 RNA, herein designated VGAM RNA, also designated SEQ ID:3459.

[29606] Another function of VGAM748 is therefore inhibition of KIAA0172 (Accession XM\_036295). Accordingly, utilities of VGAM748 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0172. Solute Carrier Family 17 (sodium-dependent inorganic phosphate cotransporter), Member 6 (SLC17A6, Accession NM\_020346) is another VGAM748 host target gene. SLC17A6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC17A6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC17A6 BINDING SITE, designated SEQ ID:21596, to the nucleotide sequence of VGAM748 RNA, herein designated VGAM RNA, also designated SEQ ID:3459.

[29607] Another function of VGAM748 is therefore inhibition of Solute Carrier Family 17 (sodium-dependent inorganic phosphate cotransporter), Member 6 (SLC17A6, Accession NM\_020346). Accordingly, utilities of VGAM748 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC17A6. LOC200488 (Accession XM\_117240) is another VGAM748 host target gene. LOC200488 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200488, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200488 BINDING SITE, designated SEQ ID:43313, to the nucleotide sequence of VGAM748 RNA, herein designated VGAM RNA, also designated SEQ ID:3459.

[29608] Another function of VGAM748 is therefore inhibition of LOC200488 (Accession XM\_117240). Accordingly, utilities of VGAM748 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200488. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 749 (VGAM749) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29609] VGAM749 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM749 was detected is described hereinabove with reference to Figs. 1–8.

[29610] VGAM749 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus.

VGAM749 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29611] VGAM749 gene encodes a VGAM749 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM749 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM749 precursor RNA is designated SEQ ID:735, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:735 is located at position 20005 relative to the genome of Bovine Coronavirus.

[29612] VGAM749 precursor RNA folds onto itself, forming VGAM749 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29613] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM749 folded precursor RNA into VGAM749 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM749 RNA is designated SEQ ID:3460, and is provided hereinbelow with reference to the sequence listing part.

[29614] VGAM749 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM749 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM749 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29615] VGAM749 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM749 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-



cleotide sequence of VGAM749 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM749 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM749 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29616] The complementary binding of VGAM749 RNA, herein designated VGAM RNA, to host target binding sites on VGAM749 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM749 host target RNA into VGAM749 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29617] It is appreciated that VGAM749 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM749 host target genes. The mRNA of each one of this plurality of VGAM749 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM749 RNA, herein designated VGAM RNA, and which when bound by VGAM749 RNA causes inhibition of translation of respective one or more VGAM749 host target proteins.

[29618] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM749 gene, herein designated VGAM GENE, on one or more VGAM749 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29619] It is yet further appreciated that a function of VGAM749 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM749 correlate with, and may be deduced from, the identity of the host target genes which VGAM749 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29620] Nucleotide sequences of the VGAM749 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM749 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM749 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM749 are further described hereinbelow with reference to Table 1.

[29621] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM749 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM749 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29622] As mentioned hereinabove with reference to Fig. 1, a function of VGAM749 gene, herein designated VGAM is inhibition of expression of VGAM749 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM749 correlate with, and may be deduced from, the identity of the target genes which VGAM749 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29623] Activin A Receptor, Type I (ACVR1, Accession NM\_001105) is a VGAM749 host target gene. ACVR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ACVR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACVR1 BINDING SITE, designated SEQ ID:6762, to the nucleotide se-

quence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29624] A function of VGAM749 is therefore inhibition of Activin A Receptor, Type I (ACVR1, Accession NM\_001105), a gene which Activin receptor-like kinase; similar to activin, TGF-beta, and C. elegans daf-1 receptors. Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACVR1. The function of ACVR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM217. Hexokinase 1 (HK1, Accession NM\_000188) is another VGAM749 host target gene. HK1 BINDING SITE1 through HK1 BINDING SITE5 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HK1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HK1 BINDING SITE1 through HK1 BINDING SITE5, designated SEQ ID:5689, SEQ ID:27267, SEQ ID:27270, SEQ ID:27273 and SEQ ID:27266 respectively, to the nucleotide sequence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29625] Another function of VGAM749 is therefore inhibition of Hexokinase 1 (HK1, Accession NM\_000188). Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HK1. Kinesin Family Member 5C (KIF5C, Accession NM\_004522) is another VGAM749 host target gene. KIF5C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIF5C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIF5C BINDING SITE, designated SEQ ID:10852, to the nucleotide sequence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29626] Another function of VGAM749 is therefore inhibition of Kinesin Family Member 5C (KIF5C, Accession NM\_004522). Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIF5C. Steroid-5-alpha-reductase, Alpha Polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) (SRD5A1, Accession NM\_001047) is another VGAM749 host target gene. SRD5A1 BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by SRD5A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRD5A1 BINDING SITE, designated SEQ ID:6714, to the nucleotide sequence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29627] Another function of VGAM749 is therefore inhibition of Steroid-5-alpha-reductase, Alpha Polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) (SRD5A1, Accession NM\_001047), a gene which catalyzes the conversion of testosterone into 5-alpha-dihydrotestosterone and progesterone . Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRD5A1. The function of SRD5A1 has been established by previous studies. Harris et al. (1992) concluded that SRD5A1 is a minor component of the reductase activity in prostate although the gene was originally cloned from prostate. On the other hand, SRD5A1 appears to be the predominant isozyme of steroid 5-alpha-reductase in the scalp and elsewhere in the skin. The possibility of scalp-selective inhibitors being

useful in the treatment of male pattern baldness, acne, and hirsutism, all 'disorders' that appear to be dihydrotestosterone dependent, was raised. Jenkins et al. (1992) used RFLPs of the SRD5A1 gene to exclude the gene as the site of the mutation in classic 5-alpha-reductase deficiency (pseudovaginal perineoscrotal hypospadias; 264600). They further showed that in contrast to the major steroid 5-alpha-reductase in the prostate and cultured skin fibroblasts, which was designated SRD5A2, the cDNA-encoded enzyme, representing SRD5A1, exhibited a neutral to basic pH optimum and was much less sensitive to inhibition by the 4-aza steroid finasteride.

[29628] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29629] Harris, G.; Azzolina, B.; Baginsky, W.; Cimis, G.; Rasmussen, G. H.; Tolman, R. L.; Raetz, C. R. H.; Ellsworth, K. : Identification and selective inhibition of an isozyme of steroid 5-alpha-reductase in human scalp. Proc. Nat. Acad. Sci. 89: 10787-10791, 1992. ; and

[29630] Jenkins, E. P.; Andersson, S.; Imperato-McGinley, J.; Wilson, J. D.; Russell, D. W. : Genetic and pharmacological



evidence for more than one human steroid

5- $\alpha$ -reductase. J. Clin. Invest.

[29631] Further studies establishing the function and utilities of SRD5A1 are found in John Hopkins OMIM database record ID 184753, and in cited publications numbered 12628-12631, 190 and 12632-12634 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. MGC13159 (Accession NM\_032927) is another VGAM749 host target gene. MGC13159 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC13159, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC13159 BINDING SITE, designated SEQ ID:26751, to the nucleotide sequence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29632] Another function of VGAM749 is therefore inhibition of MGC13159 (Accession NM\_032927). Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC13159. MGC3020 (Accession NM\_024048) is another VGAM749 host target gene. MGC3020 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC3020, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC3020 BINDING SITE, designated SEQ ID:23483, to the nucleotide sequence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29633] Another function of VGAM749 is therefore inhibition of MGC3020 (Accession NM\_024048). Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC3020. LOC146227 (Accession XM\_085374) is another VGAM749 host target gene. LOC146227 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146227, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146227 BINDING SITE, designated SEQ ID:38081, to the nucleotide sequence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29634] Another function of VGAM749 is therefore inhibition of

LOC146227 (Accession XM\_085374). Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146227. LOC151719 (Accession XM\_087280) is another VGAM749 host target gene. LOC151719 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151719, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151719 BINDING SITE, designated SEQ ID:39161, to the nucleotide sequence of VGAM749 RNA, herein designated VGAM RNA, also designated SEQ ID:3460.

[29635] Another function of VGAM749 is therefore inhibition of LOC151719 (Accession XM\_087280). Accordingly, utilities of VGAM749 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151719. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 750 (VGAM750) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[29636] VGAM750 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM750 was detected is described hereinabove with reference to Figs. 1–8.

[29637] VGAM750 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM750 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29638] VGAM750 gene encodes a VGAM750 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM750 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM750 precursor RNA is designated SEQ ID:736, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:736 is located at position 9253 relative to the genome of Bovine Coronavirus.

[29639] VGAM750 precursor RNA folds onto itself, forming VGAM750 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[29640] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM750 folded precursor RNA into VGAM750 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 44%) nucleotide se-  
quence of VGAM750 RNA is designated SEQ ID:3461, and  
is provided hereinbelow with reference to the sequence  
listing part.

[29641] VGAM750 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM750 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM750 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[29642] VGAM750 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM750 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM750 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM750 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM750 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[29643] The complementary binding of VGAM750 RNA, herein designated VGAM RNA, to host target binding sites on VGAM750 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM750 host target RNA into VGAM750 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29644] It is appreciated that VGAM750 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM750 host target genes. The mRNA of each one of this plurality of VGAM750 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM750 RNA, herein designated VGAM RNA, and which when bound by VGAM750 RNA causes inhibition of translation of respective one or more VGAM750 host target proteins.

[29645] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM750 gene, herein designated VGAM GENE, on one or

more VGAM750 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29646] It is yet further appreciated that a function of VGAM750 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM750 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM750 correlate with, and may be deduced from, the identity of the host target genes which VGAM750 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.



- [29647] Nucleotide sequences of the VGAM750 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM750 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM750 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM750 are further described hereinbelow with reference to Table 1.
- [29648] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM750 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM750 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [29649] As mentioned hereinabove with reference to Fig. 1, a function of VGAM750 gene, herein designated VGAM is inhibition of expression of VGAM750 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM750 correlate with, and may be deduced from, the identity of the target genes which VGAM750 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [29650] Reelin (RELN, Accession XM\_168628) is a VGAM750 host

target gene. RELN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RELN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RELN BINDING SITE, designated SEQ ID:45279, to the nucleotide sequence of VGAM750 RNA, herein designated VGAM RNA, also designated SEQ ID:3461.

[29651] A function of VGAM750 is therefore inhibition of Reelin (RELN, Accession XM\_168628), a gene which regulates microtubule function in neurons and neuronal migration. Accordingly, utilities of VGAM750 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RELN. The function of RELN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM35. Spinocerebellar Ataxia 7 (olivopontocerebellar atrophy with retinal degeneration) (SCA7, Accession NM\_000333) is another VGAM750 host target gene. SCA7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCA7, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCA7 BINDING SITE, designated SEQ ID:5882, to the nucleotide sequence of VGAM750 RNA, herein designated VGAM RNA, also designated SEQ ID:3461.

[29652] Another function of VGAM750 is therefore inhibition of Spinocerebellar Ataxia 7 (olivopontocerebellar atrophy with retinal degeneration) (SCA7, Accession NM\_000333). Accordingly, utilities of VGAM750 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCA7. FLJ20171 (Accession NM\_017697) is another VGAM750 host target gene. FLJ20171 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20171, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20171 BINDING SITE, designated SEQ ID:19260, to the nucleotide sequence of VGAM750 RNA, herein designated VGAM RNA, also designated SEQ ID:3461.

[29653] Another function of VGAM750 is therefore inhibition of FLJ20171 (Accession NM\_017697). Accordingly, utilities of

VGAM750 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20171. GG2-1 (Accession NM\_014350) is another VGAM750 host target gene. GG2-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GG2-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GG2-1 BINDING SITE, designated SEQ ID:15677, to the nucleotide sequence of VGAM750 RNA, herein designated VGAM RNA, also designated SEQ ID:3461.

[29654] Another function of VGAM750 is therefore inhibition of GG2-1 (Accession NM\_014350). Accordingly, utilities of VGAM750 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GG2-1. LOC132235 (Accession XM\_072302) is another VGAM750 host target gene. LOC132235 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC132235, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC132235 BINDING

SITE, designated SEQ ID:37480, to the nucleotide sequence of VGAM750 RNA, herein designated VGAM RNA, also designated SEQ ID:3461.

[29655] Another function of VGAM750 is therefore inhibition of LOC132235 (Accession XM\_072302). Accordingly, utilities of VGAM750 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC132235. LOC255104 (Accession XM\_170911) is another VGAM750 host target gene. LOC255104 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255104, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255104 BINDING SITE, designated SEQ ID:45681, to the nucleotide sequence of VGAM750 RNA, herein designated VGAM RNA, also designated SEQ ID:3461.

[29656] Another function of VGAM750 is therefore inhibition of LOC255104 (Accession XM\_170911). Accordingly, utilities of VGAM750 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255104. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 751 (VGAM751) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29657] VGAM751 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM751 was detected is described hereinabove with reference to Figs. 1–8.

[29658] VGAM751 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM751 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29659] VGAM751 gene encodes a VGAM751 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM751 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM751 precursor RNA is designated SEQ ID:737, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:737 is located at position 17776 relative to the genome of

## Bovine Coronavirus.

[29660] VGAM751 precursor RNA folds onto itself, forming VGAM751 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29661] An enzyme complex designated DICER COMPLEX, `dices` the VGAM751 folded precursor RNA into VGAM751 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM751 RNA is designated SEQ ID:3462, and is provided hereinbelow with reference to the sequence listing part.

[29662] VGAM751 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM751 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM751 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29663] VGAM751 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM751 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM751 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM751 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM751 host target RNA, herein designated VGAM HOST TARGET RNA. It is further



appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29664] The complementary binding of VGAM751 RNA, herein designated VGAM RNA, to host target binding sites on VGAM751 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM751 host target RNA into VGAM751 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29665] It is appreciated that VGAM751 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM751 host target genes. The mRNA of each one of this plurality of VGAM751 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM751 RNA, herein designated VGAM RNA, and which when bound by VGAM751 RNA causes inhibition of translation of respective one or more VGAM751 host target proteins.

[29666] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM751 gene, herein designated VGAM GENE, on one or more VGAM751 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29667] It is yet further appreciated that a function of VGAM751 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM751 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM751 correlate

with, and may be deduced from, the identity of the host target genes which VGAM751 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29668] Nucleotide sequences of the VGAM751 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM751 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM751 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM751 are further described hereinbelow with reference to Table 1.

[29669] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM751 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM751 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29670] As mentioned hereinabove with reference to Fig. 1, a function of VGAM751 gene, herein designated VGAM is inhibition of expression of VGAM751 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM751 correlate with, and may be deduced

from, the identity of the target genes which VGAM751 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29671] Chemokine (C-X3-C motif) Receptor 1 (CX3CR1, Accession XM\_047502) is a VGAM751 host target gene. CX3CR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CX3CR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CX3CR1 BINDING SITE, designated SEQ ID:34976, to the nucleotide sequence of VGAM751 RNA, herein designated VGAM RNA, also designated SEQ ID:3462.

[29672] A function of VGAM751 is therefore inhibition of Chemokine (C-X3-C motif) Receptor 1 (CX3CR1, Accession XM\_047502), a gene which mediates both the adhesive and migratory functions of fractalkine. Accordingly, utilities of VGAM751 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CX3CR1. The function of CX3CR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove

with reference to VGAM25.Oxidation Resistance 1 (OXR1, Accession NM\_018002) is another VGAM751 host target gene. OXR1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by OXR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OXR1 BINDING SITE, designated SEQ ID:19732, to the nucleotide sequence of VGAM751 RNA, herein designated VGAM RNA, also designated SEQ ID:3462.

[29673] Another function of VGAM751 is therefore inhibition of Oxidation Resistance 1 (OXR1, Accession NM\_018002). Accordingly, utilities of VGAM751 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OXR1. KIAA1036 (Accession NM\_014909) is another VGAM751 host target gene. KIAA1036 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1036, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1036 BINDING SITE, designated SEQ ID:17122, to the nucleotide sequence of VGAM751 RNA, herein designated

VGAM RNA, also designated SEQ ID:3462.

[29674] Another function of VGAM751 is therefore inhibition of KIAA1036 (Accession NM\_014909). Accordingly, utilities of VGAM751 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1036. LOC120856 (Accession XM\_058509) is another VGAM751 host target gene. LOC120856 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC120856, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120856 BINDING SITE, designated SEQ ID:36644, to the nucleotide sequence of VGAM751 RNA, herein designated VGAM RNA, also designated SEQ ID:3462.

[29675] Another function of VGAM751 is therefore inhibition of LOC120856 (Accession XM\_058509). Accordingly, utilities of VGAM751 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120856. LOC221474 (Accession XM\_166464) is another VGAM751 host target gene. LOC221474 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221474, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221474 BINDING SITE, designated SEQ ID:44379, to the nucleotide sequence of VGAM751 RNA, herein designated VGAM RNA, also designated SEQ ID:3462.

[29676] Another function of VGAM751 is therefore inhibition of LOC221474 (Accession XM\_166464). Accordingly, utilities of VGAM751 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221474. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 752 (VGAM752) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29677] VGAM752 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM752 was detected is described hereinabove with reference to Figs. 1–8.

[29678] VGAM752 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus.

VGAM752 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29679] VGAM752 gene encodes a VGAM752 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM752 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM752 precursor RNA is designated SEQ ID:738, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:738 is located at position 18144 relative to the genome of Bovine Coronavirus.

[29680] VGAM752 precursor RNA folds onto itself, forming VGAM752 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29681] An enzyme complex designated DICER COMPLEX, `dices`



the VGAM752 folded precursor RNA into VGAM752 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM752 RNA is designated SEQ ID:3463, and is provided hereinbelow with reference to the sequence listing part.

[29682] VGAM752 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM752 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM752 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29683] VGAM752 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM752 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM752 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM752 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM752 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29684] The complementary binding of VGAM752 RNA, herein designated VGAM RNA, to host target binding sites on VGAM752 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM752 host target RNA into VGAM752 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29685] It is appreciated that VGAM752 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM752 host target genes. The mRNA of each one of this plurality of VGAM752 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM752 RNA, herein designated VGAM RNA, and which when bound by VGAM752 RNA causes inhibition of translation of respective one or more VGAM752 host target proteins.

[29686] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM752 gene, herein designated VGAM GENE, on one or more VGAM752 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29687] It is yet further appreciated that a function of VGAM752 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM752 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM752 correlate with, and may be deduced from, the identity of the host target genes which VGAM752 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29688] Nucleotide sequences of the VGAM752 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM752 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM752 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM752 are further described hereinbelow with reference to Table 1.

[29689] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM752 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM752 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29690] As mentioned hereinabove with reference to Fig. 1, a function of VGAM752 gene, herein designated VGAM is inhibition of expression of VGAM752 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM752 correlate with, and may be deduced from, the identity of the target genes which VGAM752 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29691] ATPase, Aminophospholipid Transporter-like, Class I, Type 8A, Member 2 (ATP8A2, Accession XM\_167916) is a VGAM752 host target gene. ATP8A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP8A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP8A2 BINDING

SITE, designated SEQ ID:44916, to the nucleotide sequence of VGAM752 RNA, herein designated VGAM RNA, also designated SEQ ID:3463.

[29692] A function of VGAM752 is therefore inhibition of ATPase, Aminophospholipid Transporter-like, Class I, Type 8A, Member 2 (ATP8A2, Accession XM\_167916). Accordingly, utilities of VGAM752 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP8A2. KIAA1229 (Accession XM\_030665) is another VGAM752 host target gene. KIAA1229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1229 BINDING SITE, designated SEQ ID:31099, to the nucleotide sequence of VGAM752 RNA, herein designated VGAM RNA, also designated SEQ ID:3463.

[29693] Another function of VGAM752 is therefore inhibition of KIAA1229 (Accession XM\_030665). Accordingly, utilities of VGAM752 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1229. KIAA1509 (Accession XM\_029353) is another

VGAM752 host target gene. KIAA1509 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1509, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1509 BINDING SITE, designated SEQ ID:30871, to the nucleotide sequence of VGAM752 RNA, herein designated VGAM RNA, also designated SEQ ID:3463.

[29694] Another function of VGAM752 is therefore inhibition of KIAA1509 (Accession XM\_029353). Accordingly, utilities of VGAM752 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1509. Ubc6p (Accession NM\_058167) is another VGAM752 host target gene. Ubc6p BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by Ubc6p, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Ubc6p BINDING SITE, designated SEQ ID:27714, to the nucleotide sequence of VGAM752 RNA, herein designated VGAM RNA, also designated SEQ ID:3463.

[29695] Another function of VGAM752 is therefore inhibition of Ubc6p (Accession NM\_058167). Accordingly, utilities of VGAM752 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Ubc6p. LOC165904 (Accession XM\_093522) is another VGAM752 host target gene. LOC165904 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC165904, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC165904 BINDING SITE, designated SEQ ID:40194, to the nucleotide sequence of VGAM752 RNA, herein designated VGAM RNA, also designated SEQ ID:3463.

[29696] Another function of VGAM752 is therefore inhibition of LOC165904 (Accession XM\_093522). Accordingly, utilities of VGAM752 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC165904. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 753 (VGAM753) viral gene, which modulates expression of respective host target genes thereof,



the function and utility of which host target genes is known in the art.

[29697] VGAM753 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM753 was detected is described hereinabove with reference to Figs. 1–8.

[29698] VGAM753 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM753 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29699] VGAM753 gene encodes a VGAM753 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM753 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM753 precursor RNA is designated SEQ ID:739, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:739 is located at position 10788 relative to the genome of Bovine Coronavirus.

[29700] VGAM753 precursor RNA folds onto itself, forming VGAM753 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[29701] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM753 folded precursor RNA into VGAM753 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 47%) nucleotide se-  
quence of VGAM753 RNA is designated SEQ ID:3464, and  
is provided hereinbelow with reference to the sequence  
listing part.

[29702] VGAM753 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM753 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM753 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29703] VGAM753 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM753 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM753 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM753 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM753 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29704] The complementary binding of VGAM753 RNA, herein designated VGAM RNA, to host target binding sites on VGAM753 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM753 host target RNA into VGAM753 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29705] It is appreciated that VGAM753 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM753 host target genes. The mRNA of each one of this plurality of VGAM753 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM753 RNA, herein designated VGAM RNA, and which when bound by VGAM753 RNA causes inhibition of translation of respective one or more VGAM753 host target proteins.

[29706] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM753 gene, herein designated VGAM GENE, on one or more VGAM753 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29707] It is yet further appreciated that a function of VGAM753 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM753 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM753 correlate with, and may be deduced from, the identity of the host target genes which VGAM753 binds and inhibits, and the function of these host target genes, as elaborated herein—

below.

- [29708] Nucleotide sequences of the VGAM753 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM753 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM753 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM753 are further described hereinbelow with reference to Table 1.
- [29709] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM753 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM753 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [29710] As mentioned hereinabove with reference to Fig. 1, a function of VGAM753 gene, herein designated VGAM is inhibition of expression of VGAM753 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM753 correlate with, and may be deduced from, the identity of the target genes which VGAM753 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29711] EDR1 (Accession NM\_004426) is a VGAM753 host target gene. EDR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EDR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EDR1 BINDING SITE, designated SEQ ID:10702, to the nucleotide sequence of VGAM753 RNA, herein designated VGAM RNA, also designated SEQ ID:3464.

[29712] A function of VGAM753 is therefore inhibition of EDR1 (Accession NM\_004426). Accordingly, utilities of VGAM753 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EDR1. KIAA1423 (Accession XM\_029703) is another VGAM753 host target gene. KIAA1423 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1423 BINDING SITE, designated SEQ ID:30921, to the nucleotide sequence of VGAM753 RNA, herein designated VGAM RNA, also designated SEQ ID:3464.

[29713] Another function of VGAM753 is therefore inhibition of KIAA1423 (Accession XM\_029703). Accordingly, utilities of VGAM753 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1423. LOC149844 (Accession XM\_086675) is another VGAM753 host target gene. LOC149844 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149844, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149844 BINDING SITE, designated SEQ ID:38822, to the nucleotide sequence of VGAM753 RNA, herein designated VGAM RNA, also designated SEQ ID:3464.

[29714] Another function of VGAM753 is therefore inhibition of LOC149844 (Accession XM\_086675). Accordingly, utilities of VGAM753 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149844. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 754 (VGAM754) viral gene, which modulates expression of respective host target genes thereof,



the function and utility of which host target genes is known in the art.

[29715] VGAM754 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM754 was detected is described hereinabove with reference to Figs. 1–8.

[29716] VGAM754 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM754 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29717] VGAM754 gene encodes a VGAM754 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM754 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM754 precursor RNA is designated SEQ ID:740, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:740 is located at position 8401 relative to the genome of Bovine Coronavirus.

[29718] VGAM754 precursor RNA folds onto itself, forming VGAM754 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[29719] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM754 folded precursor RNA into VGAM754 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 70%) nucleotide se-  
quence of VGAM754 RNA is designated SEQ ID:3465, and  
is provided hereinbelow with reference to the sequence  
listing part.

[29720] VGAM754 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM754 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM754 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29721] VGAM754 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM754 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM754 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM754 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM754 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29722] The complementary binding of VGAM754 RNA, herein designated VGAM RNA, to host target binding sites on VGAM754 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM754 host target RNA into VGAM754 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29723] It is appreciated that VGAM754 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM754 host target genes. The mRNA of each one of this plurality of VGAM754 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM754 RNA, herein designated VGAM RNA, and which when bound by VGAM754 RNA causes inhibition of translation of respective one or more VGAM754 host target proteins.

[29724] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM754 gene, herein designated VGAM GENE, on one or more VGAM754 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29725] It is yet further appreciated that a function of VGAM754 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM754 correlate with, and may be deduced from, the identity of the host target genes which VGAM754 binds and inhibits, and the function of these host target genes, as elaborated herein—

below.

- [29726] Nucleotide sequences of the VGAM754 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM754 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM754 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM754 are further described hereinbelow with reference to Table 1.
- [29727] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM754 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM754 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [29728] As mentioned hereinabove with reference to Fig. 1, a function of VGAM754 gene, herein designated VGAM is inhibition of expression of VGAM754 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM754 correlate with, and may be deduced from, the identity of the target genes which VGAM754 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29729] Runt-related Transcription Factor 1 (acute myeloid leukemia 1; aml1 oncogene) (RUNX1, Accession NM\_001754) is a VGAM754 host target gene. RUNX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RUNX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RUNX1 BINDING SITE, designated SEQ ID:7493, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29730] A function of VGAM754 is therefore inhibition of Runt-related Transcription Factor 1 (acute myeloid leukemia 1; aml1 oncogene) (RUNX1, Accession NM\_001754). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RUNX1. 1-acylglycerol-3-phosphate O-acyltransferase 1 (lysophosphatidic acid acyltransferase, alpha) (AGPAT1, Accession NM\_006411) is another VGAM754 host target gene. AGPAT1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by AGPAT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AGPAT1 BINDING SITE, designated SEQ ID:13117, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29731] Another function of VGAM754 is therefore inhibition of 1-acylglycerol-3-phosphate O-acyltransferase 1 (lysophosphatidic acid acyltransferase, alpha) (AGPAT1, Accession NM\_006411). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AGPAT1. DKFZP434E2135 (Accession NM\_030804) is another VGAM754 host target gene. DKFZP434E2135 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZP434E2135, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434E2135 BINDING SITE, designated SEQ ID:25112, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29732] Another function of VGAM754 is therefore inhibition of



DKFZP434E2135 (Accession NM\_030804). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434E2135. M-phase Phosphoprotein 10 (U3 small nucleolar ribonucleoprotein) (MPHOSPH10, Accession XM\_030865) is another VGAM754 host target gene. MPHOSPH10 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MPHOSPH10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MPHOSPH10 BINDING SITE, designated SEQ ID:31204, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29733] Another function of VGAM754 is therefore inhibition of M-phase Phosphoprotein 10 (U3 small nucleolar ribonucleoprotein) (MPHOSPH10, Accession XM\_030865). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MPHOSPH10. RENT2 (Accession NM\_080599) is another VGAM754 host target gene. RENT2 BINDING SITE1 and RENT2 BINDING SITE2 are HOST TARGET bind-

ing sites found in untranslated regions of mRNA encoded by RENT2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RENT2 BINDING SITE1 and RENT2 BINDING SITE2, designated SEQ ID:27909 and SEQ ID:17803 respectively, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29734] Another function of VGAM754 is therefore inhibition of RENT2 (Accession NM\_080599). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RENT2. LOC146332 (Accession XM\_085413) is another VGAM754 host target gene. LOC146332 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146332, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146332 BINDING SITE, designated SEQ ID:38129, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29735] Another function of VGAM754 is therefore inhibition of LOC146332 (Accession XM\_085413). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146332. LOC150519 (Accession XM\_086937) is another VGAM754 host target gene. LOC150519 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150519 BINDING SITE, designated SEQ ID:38987, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29736] Another function of VGAM754 is therefore inhibition of LOC150519 (Accession XM\_086937). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150519. LOC196446 (Accession XM\_113722) is another VGAM754 host target gene. LOC196446 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196446, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196446 BINDING SITE, designated SEQ ID:42371, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29737] Another function of VGAM754 is therefore inhibition of LOC196446 (Accession XM\_113722). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196446. LOC90233 (Accession NM\_138347) is another VGAM754 host target gene. LOC90233 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90233, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90233 BINDING SITE, designated SEQ ID:28744, to the nucleotide sequence of VGAM754 RNA, herein designated VGAM RNA, also designated SEQ ID:3465.

[29738] Another function of VGAM754 is therefore inhibition of LOC90233 (Accession NM\_138347). Accordingly, utilities of VGAM754 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC90233. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 755 (VGAM755) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29739] VGAM755 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM755 was detected is described hereinabove with reference to Figs. 1–8.

[29740] VGAM755 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM755 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29741] VGAM755 gene encodes a VGAM755 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM755 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM755 precursor RNA is designated SEQ ID:741, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:741 is located at position 5925 relative to the genome of Bovine Coronavirus.

[29742] VGAM755 precursor RNA folds onto itself, forming VGAM755 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29743] An enzyme complex designated DICER COMPLEX, `dices` the VGAM755 folded precursor RNA into VGAM755 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 59%) nucleotide sequence of VGAM755 RNA is designated SEQ ID:3466, and is provided hereinbelow with reference to the sequence listing part.

[29744] VGAM755 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM755 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM755 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29745] VGAM755 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM755 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM755 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM755 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM755 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[29746] The complementary binding of VGAM755 RNA, herein designated VGAM RNA, to host target binding sites on VGAM755 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM755 host target RNA into VGAM755 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29747] It is appreciated that VGAM755 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM755 host target genes. The mRNA of each one of this plurality of VGAM755 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM755 RNA, herein designated VGAM RNA, and which when bound by VGAM755 RNA causes in-



hibition of translation of respective one or more VGAM755 host target proteins.

[29748] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM755 gene, herein designated VGAM GENE, on one or more VGAM755 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29749] It is yet further appreciated that a function of VGAM755 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM755 include diagnosis, prevention and

treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM755 correlate with, and may be deduced from, the identity of the host target genes which VGAM755 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29750] Nucleotide sequences of the VGAM755 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM755 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM755 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM755 are further described hereinbelow with reference to Table 1.

[29751] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM755 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM755 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29752] As mentioned hereinabove with reference to Fig. 1, a function of VGAM755 gene, herein designated VGAM is inhibition of expression of VGAM755 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM755 correlate with, and may be deduced from, the identity of the target genes which VGAM755 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29753] GDP Dissociation Inhibitor 2 (GDI2, Accession NM\_001494) is a VGAM755 host target gene. GDI2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GDI2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GDI2 BINDING SITE, designated SEQ ID:7241, to the nucleotide sequence of VGAM755 RNA, herein designated VGAM RNA, also designated SEQ ID:3466.

[29754] A function of VGAM755 is therefore inhibition of GDP Dissociation Inhibitor 2 (GDI2, Accession NM\_001494), a gene which regulates the gdp/gtp exchange reaction of most rab proteins by inhibiting the dissociation of gdp from them, and the subsequent binding of gtp to them. Accordingly, utilities of VGAM755 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GDI2. The function of GDI2 has been es-

established by previous studies. Various rab GDI-beta (RABGDIB) genes have been identified in a variety of species. It is a member of the GDP-dissociation inhibitor family, which includes GDI-alpha (RABGDIA; 300104). Shisheva et al. (1994) cloned mouse RABGDIB (which they referred to as 'smg p25A GDI') and reported the sequence. Sedlacek et al. (1995) found that the human RABGDIB sequence is 86.5% similar to RABGDIA, which they referred to as 'XAP-4.' Bachner et al. (1995) studied expression patterns of the 2 human genes. They showed that the 2.5-kb mRNA for RABGDIB is ubiquitously expressed, in contrast to RABGDIA, which is expressed primarily in neural and sensory tissues. By in situ hybridization, Sedlacek et al. (1998) demonstrated that the GDI2 gene maps to 10p15; a processed pseudogene mapped to 7p13-p11.

[29755] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29756] Sedlacek, Z.; Munstermann, E.; Mincheva, A.; Lichter, P.; Poustka, A. : The human rab GDI beta gene with long retroposon-rich introns maps to 10p15 and its pseudogene to 7p11-p13. Mammalian Genome 9: 78-80, 1998. ; and

[29757] Shisheva, A.; Sudhof, T. C.; Czech, M. P. : Cloning, characterization, and expression of a novel GDP dissociation inhibitor isoform from skeletal muscle. *Molec. Cell. Biol.* 14: 3459–346.

[29758] Further studies establishing the function and utilities of GDI2 are found in John Hopkins OMIM database record ID 600767, and in cited publications numbered 8799, 9601–960 and 9062 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 20 Open Reading Frame 43 (C20orf43, Accession XM\_009549) is another VGAM755 host target gene. C20orf43 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf43, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf43 BINDING SITE, designated SEQ ID:30112, to the nucleotide sequence of VGAM755 RNA, herein designated VGAM RNA, also designated SEQ ID:3466.

[29759] Another function of VGAM755 is therefore inhibition of Chromosome 20 Open Reading Frame 43 (C20orf43, Accession XM\_009549). Accordingly, utilities of VGAM755

include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf43. Chromosome 20 Open Reading Frame 82 (C20orf82, Accession XM\_097736) is another VGAM755 host target gene.

C20orf82 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf82, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf82 BINDING SITE, designated SEQ ID:41085, to the nucleotide sequence of VGAM755 RNA, herein designated VGAM RNA, also designated SEQ ID:3466.

[29760] Another function of VGAM755 is therefore inhibition of Chromosome 20 Open Reading Frame 82 (C20orf82, Accession XM\_097736). Accordingly, utilities of VGAM755 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf82. MGC12966 (Accession NM\_032706) is another VGAM755 host target gene. MGC12966 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC12966, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC12966 BINDING SITE, designated SEQ ID:26418, to the nucleotide sequence of VGAM755 RNA, herein designated VGAM RNA, also designated SEQ ID:3466.

[29761] Another function of VGAM755 is therefore inhibition of MGC12966 (Accession NM\_032706). Accordingly, utilities of VGAM755 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC12966. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 756 (VGAM756) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29762] VGAM756 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM756 was detected is described hereinabove with reference to Figs. 1–8.

[29763] VGAM756 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM756 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[29764] VGAM756 gene encodes a VGAM756 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM756 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM756 precursor RNA is designated SEQ ID:742, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:742 is located at position 15954 relative to the genome of Bovine Coronavirus.

[29765] VGAM756 precursor RNA folds onto itself, forming VGAM756 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29766] An enzyme complex designated DICER COMPLEX, `dices` the VGAM756 folded precursor RNA into VGAM756 RNA,



herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM756 RNA is designated SEQ ID:3467, and is provided hereinbelow with reference to the sequence listing part.

[29767] VGAM756 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM756 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM756 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29768] VGAM756 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM756 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM756 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM756 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM756 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29769] The complementary binding of VGAM756 RNA, herein designated VGAM RNA, to host target binding sites on VGAM756 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM756 host target RNA into VGAM756 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[29770] It is appreciated that VGAM756 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM756 host target genes. The mRNA of each one of this plurality of VGAM756 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM756 RNA, herein designated VGAM RNA, and which when bound by VGAM756 RNA causes inhibition of translation of respective one or more VGAM756 host target proteins.

[29771] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM756 gene, herein designated VGAM GENE, on one or more VGAM756 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29772] It is yet further appreciated that a function of VGAM756 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM756 correlate with, and may be deduced from, the identity of the host target genes which VGAM756 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29773] Nucleotide sequences of the VGAM756 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM756 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM756 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM756 are further described hereinbelow with reference to Table 1.

[29774] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM756 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM756 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29775] As mentioned hereinabove with reference to Fig. 1, a function of VGAM756 gene, herein designated VGAM is inhibition of expression of VGAM756 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM756 correlate with, and may be deduced from, the identity of the target genes which VGAM756 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29776] Ubiquitin-conjugating Enzyme E2L 3 (UBE2L3, Accession NM\_003347) is a VGAM756 host target gene. UBE2L3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2L3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2L3 BINDING SITE, designated SEQ ID:9354, to the nucleotide sequence of VGAM756 RNA, herein designated

VGAM RNA, also designated SEQ ID:3467.

[29777] A function of VGAM756 is therefore inhibition of Ubiquitin-conjugating Enzyme E2L 3 (UBE2L3, Accession NM\_003347), a gene which catalyzes the covalent attachment of ubiquitin to other proteins. Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2L3. The function of UBE2L3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM215. Angiomotin (AMOT, Accession NM\_133265) is another VGAM756 host target gene. AMOT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AMOT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AMOT BINDING SITE, designated SEQ ID:28416, to the nucleotide sequence of VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29778] Another function of VGAM756 is therefore inhibition of Angiomotin (AMOT, Accession NM\_133265). Accordingly, utilities of VGAM756 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with AMOT. FLJ13195 (Accession NM\_022906) is another VGAM756 host target gene. FLJ13195 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13195, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13195 BINDING SITE, designated SEQ ID:23203, to the nucleotide sequence of VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29779] Another function of VGAM756 is therefore inhibition of FLJ13195 (Accession NM\_022906). Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13195. FLJ23132 (Accession XM\_171194) is another VGAM756 host target gene. FLJ23132 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23132, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23132 BINDING SITE, designated SEQ ID:45983, to the nucleotide sequence of

VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29780] Another function of VGAM756 is therefore inhibition of FLJ23132 (Accession XM\_171194). Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23132. HSPC039 (Accession NM\_016097) is another VGAM756 host target gene. HSPC039 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPC039, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC039 BINDING SITE, designated SEQ ID:18180, to the nucleotide sequence of VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29781] Another function of VGAM756 is therefore inhibition of HSPC039 (Accession NM\_016097). Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC039. PTPRF Interacting Protein, Binding Protein 1 (liprin beta 1) (PPFIBP1, Accession NM\_003622) is another VGAM756 host target gene. PPFIBP1 BINDING SITE is HOST TARGET



binding site found in the 3' untranslated region of mRNA encoded by PPFIBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPFIBP1 BINDING SITE, designated SEQ ID:9685, to the nucleotide sequence of VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29782] Another function of VGAM756 is therefore inhibition of PTPRF Interacting Protein, Binding Protein 1 (liprin beta 1) (PPFIBP1, Accession NM\_003622). Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPFIBP1. PR Domain Containing 8 (PRDM8, Accession NM\_020226) is another VGAM756 host target gene. PRDM8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRDM8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRDM8 BINDING SITE, designated SEQ ID:21488, to the nucleotide sequence of VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29783] Another function of VGAM756 is therefore inhibition of PR Domain Containing 8 (PRDM8, Accession NM\_020226). Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRDM8. LOC122726 (Accession XM\_063296) is another VGAM756 host target gene. LOC122726 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC122726, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC122726 BINDING SITE, designated SEQ ID:37236, to the nucleotide sequence of VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29784] Another function of VGAM756 is therefore inhibition of LOC122726 (Accession XM\_063296). Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC122726. LOC83690 (Accession NM\_031461) is another VGAM756 host target gene. LOC83690 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC83690, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC83690 BINDING SITE, designated SEQ ID:25485, to the nucleotide sequence of VGAM756 RNA, herein designated VGAM RNA, also designated SEQ ID:3467.

[29785] Another function of VGAM756 is therefore inhibition of LOC83690 (Accession NM\_031461). Accordingly, utilities of VGAM756 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC83690. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 757 (VGAM757) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29786] VGAM757 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM757 was detected is described hereinabove with reference to Figs. 1–8.

[29787] VGAM757 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus.

VGAM757 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29788] VGAM757 gene encodes a VGAM757 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM757 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM757 precursor RNA is designated SEQ ID:743, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:743 is located at position 378 relative to the genome of Bovine Coronavirus.

[29789] VGAM757 precursor RNA folds onto itself, forming VGAM757 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29790] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM757 folded precursor RNA into VGAM757 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 52%) nucleotide sequence of VGAM757 RNA is designated SEQ ID:3468, and is provided hereinbelow with reference to the sequence listing part.

[29791] VGAM757 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM757 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM757 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29792] VGAM757 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM757 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM757 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM757 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM757 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29793] The complementary binding of VGAM757 RNA, herein designated VGAM RNA, to host target binding sites on VGAM757 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM757 host target RNA into VGAM757 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29794] It is appreciated that VGAM757 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM757 host target genes. The mRNA of each one of this plurality of VGAM757 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM757 RNA, herein designated VGAM RNA, and which when bound by VGAM757 RNA causes inhibition of translation of respective one or more VGAM757 host target proteins.

[29795] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM757 gene, herein designated VGAM GENE, on one or more VGAM757 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29796] It is yet further appreciated that a function of VGAM757 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM757 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM757 correlate with, and may be deduced from, the identity of the host target genes which VGAM757 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29797] Nucleotide sequences of the VGAM757 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM757 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM757 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM757 are further described hereinbelow with reference to Table 1.



[29798] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM757 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM757 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29799] As mentioned hereinabove with reference to Fig. 1, a function of VGAM757 gene, herein designated VGAM is inhibition of expression of VGAM757 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM757 correlate with, and may be deduced from, the identity of the target genes which VGAM757 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29800] Zinc Finger Protein 207 (ZNF207, Accession NM\_003457) is a VGAM757 host target gene. ZNF207 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF207, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF207 BINDING SITE, designated SEQ ID:9515, to the nucleotide

sequence of VGAM757 RNA, herein designated VGAM RNA, also designated SEQ ID:3468.

[29801] A function of VGAM757 is therefore inhibition of Zinc Finger Protein 207 (ZNF207, Accession NM\_003457). Accordingly, utilities of VGAM757 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF207. FLJ23309 (Accession NM\_024896) is another VGAM757 host target gene. FLJ23309 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23309, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23309 BINDING SITE, designated SEQ ID:24381, to the nucleotide sequence of VGAM757 RNA, herein designated VGAM RNA, also designated SEQ ID:3468.

[29802] Another function of VGAM757 is therefore inhibition of FLJ23309 (Accession NM\_024896). Accordingly, utilities of VGAM757 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23309. Sprouty Homolog 1, Antagonist of FGF Signaling (Drosophila) (SPRY1, Accession XM\_036349) is another VGAM757 host target gene. SPRY1 BINDING SITE is HOST

TARGET binding site found in the 5` untranslated region of mRNA encoded by SPRY1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPRY1 BINDING SITE, designated SEQ ID:32429, to the nucleotide sequence of VGAM757 RNA, herein designated VGAM RNA, also designated SEQ ID:3468.

[29803] Another function of VGAM757 is therefore inhibition of Sprouty Homolog 1, Antagonist of FGF Signaling (Drosophila) (SPRY1, Accession XM\_036349). Accordingly, utilities of VGAM757 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPRY1. LOC91431 (Accession NM\_138698) is another VGAM757 host target gene. LOC91431 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC91431, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91431 BINDING SITE, designated SEQ ID:28948, to the nucleotide sequence of VGAM757 RNA, herein designated VGAM RNA, also designated SEQ ID:3468.

[29804] Another function of VGAM757 is therefore inhibition of LOC91431 (Accession NM\_138698). Accordingly, utilities of VGAM757 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91431. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 758 (VGAM758) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29805] VGAM758 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM758 was detected is described hereinabove with reference to Figs. 1–8.

[29806] VGAM758 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM758 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29807] VGAM758 gene encodes a VGAM758 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM758

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM758 precursor RNA is designated SEQ ID:744, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:744 is located at position 14862 relative to the genome of Bovine Coronavirus.

[29808] VGAM758 precursor RNA folds onto itself, forming VGAM758 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29809] An enzyme complex designated DICER COMPLEX, `dices` the VGAM758 folded precursor RNA into VGAM758 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 47%) nucleotide sequence of VGAM758 RNA is designated SEQ ID:3469, and is provided hereinbelow with reference to the sequence listing part.

[29810] VGAM758 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM758 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM758 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[29811] VGAM758 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM758 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM758 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM758 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM758 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29812] The complementary binding of VGAM758 RNA, herein designated VGAM RNA, to host target binding sites on VGAM758 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM758 host target RNA into VGAM758 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29813] It is appreciated that VGAM758 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM758 host target genes. The mRNA of each one of this plurality of VGAM758 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM758 RNA, herein designated VGAM RNA, and which when bound by VGAM758 RNA causes inhibition of translation of respective one or more VGAM758 host target proteins.

[29814] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM758 gene, herein designated VGAM GENE, on one or more VGAM758 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).



[29815] It is yet further appreciated that a function of VGAM758 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM758 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM758 correlate with, and may be deduced from, the identity of the host target genes which VGAM758 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29816] Nucleotide sequences of the VGAM758 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM758 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM758 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM758 are further described hereinbelow with reference to Table 1.

[29817] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM758 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM758 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[29818] As mentioned hereinabove with reference to Fig. 1, a function of VGAM758 gene, herein designated VGAM is inhibition of expression of VGAM758 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM758 correlate with, and may be deduced from, the identity of the target genes which VGAM758 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29819] Polycystic Kidney and Hepatic Disease 1 (autosomal recessive) (PKHD1, Accession NM\_138694) is a VGAM758 host target gene. PKHD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PKHD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PKHD1 BINDING SITE, designated SEQ ID:28945, to the nucleotide sequence of VGAM758 RNA, herein designated VGAM RNA, also designated SEQ ID:3469.

[29820] A function of VGAM758 is therefore inhibition of Polycystic Kidney and Hepatic Disease 1 (autosomal recessive) (PKHD1, Accession NM\_138694). Accordingly, utilities of

VGAM758 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PKHD1. RNA (guanine-7-) Methyltransferase (RNMT, Accession NM\_003799) is another VGAM758 host target gene. RNMT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNMT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNMT BINDING SITE, designated SEQ ID:9893, to the nucleotide sequence of VGAM758 RNA, herein designated VGAM RNA, also designated SEQ ID:3469.

[29821] Another function of VGAM758 is therefore inhibition of RNA (guanine-7-) Methyltransferase (RNMT, Accession NM\_003799), a gene which catalyzes the methylation of GpppN- at the guanine N7 position. Accordingly, utilities of VGAM758 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNMT. The function of RNMT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178.FLJ23056 (Accession NM\_024582) is another VGAM758 host target gene. FLJ23056 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23056 BINDING SITE, designated SEQ ID:23807, to the nucleotide sequence of VGAM758 RNA, herein designated VGAM RNA, also designated SEQ ID:3469.

[29822] Another function of VGAM758 is therefore inhibition of FLJ23056 (Accession NM\_024582). Accordingly, utilities of VGAM758 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23056. IPT (Accession NM\_017646) is another VGAM758 host target gene. IPT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IPT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IPT BINDING SITE, designated SEQ ID:19151, to the nucleotide sequence of VGAM758 RNA, herein designated VGAM RNA, also designated SEQ ID:3469.

[29823] Another function of VGAM758 is therefore inhibition of IPT (Accession NM\_017646). Accordingly, utilities of

VGAM758 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IPT.

MDS028 (Accession NM\_018463) is another VGAM758 host target gene. MDS028 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MDS028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MDS028 BINDING SITE, designated SEQ ID:20535, to the nucleotide sequence of VGAM758 RNA, herein designated VGAM RNA, also designated SEQ ID:3469.

[29824] Another function of VGAM758 is therefore inhibition of MDS028 (Accession NM\_018463). Accordingly, utilities of VGAM758 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MDS028. LOC137492 (Accession XM\_059910) is another VGAM758 host target gene. LOC137492 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC137492, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC137492 BINDING

SITE, designated SEQ ID:37107, to the nucleotide sequence of VGAM758 RNA, herein designated VGAM RNA, also designated SEQ ID:3469.

[29825] Another function of VGAM758 is therefore inhibition of LOC137492 (Accession XM\_059910). Accordingly, utilities of VGAM758 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC137492. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 759 (VGAM759) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29826] VGAM759 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM759 was detected is described hereinabove with reference to Figs. 1–8.

[29827] VGAM759 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM759 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29828] VGAM759 gene encodes a VGAM759 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM759 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM759 precursor RNA is designated SEQ ID:745, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:745 is located at position 7762 relative to the genome of Bovine Coronavirus.

[29829] VGAM759 precursor RNA folds onto itself, forming VGAM759 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29830] An enzyme complex designated DICER COMPLEX, `dices` the VGAM759 folded precursor RNA into VGAM759 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM759 RNA is designated SEQ ID:3470, and is provided hereinbelow with reference to the sequence listing part.

[29831] VGAM759 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM759 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM759 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29832] VGAM759 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM759 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM759 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-



illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM759 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM759 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29833] The complementary binding of VGAM759 RNA, herein designated VGAM RNA, to host target binding sites on VGAM759 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM759 host target RNA into VGAM759 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29834] It is appreciated that VGAM759 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM759 host target genes. The mRNA of each one of this plurality of VGAM759 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM759 RNA, herein designated VGAM RNA, and which when bound by VGAM759 RNA causes inhibition of translation of respective one or more VGAM759 host target proteins.

[29835] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM759 gene, herein designated VGAM GENE, on one or more VGAM759 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[29836] It is yet further appreciated that a function of VGAM759 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM759 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM759 correlate with, and may be deduced from, the identity of the host target genes which VGAM759 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29837] Nucleotide sequences of the VGAM759 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM759 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM759 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM759 are further described hereinbelow with reference to Table 1.

[29838] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM759 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM759 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29839] As mentioned hereinabove with reference to Fig. 1, a function of VGAM759 gene, herein designated VGAM is inhibition of expression of VGAM759 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM759 correlate with, and may be deduced from, the identity of the target genes which VGAM759 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29840] Transient Receptor Potential Cation Channel, Subfamily C, Member 5 (TRPC5, Accession NM\_012471) is a VGAM759 host target gene. TRPC5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPC5 BINDING SITE, designated SEQ ID:14849, to the nucleotide sequence of VGAM759 RNA, herein designated VGAM RNA, also designated SEQ ID:3470.

[29841] A function of VGAM759 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily C, Member 5 (TRPC5, Accession NM\_012471). Accordingly, utilities of VGAM759 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPC5. KIAA0090 (Accession XM\_114045) is another VGAM759 host target gene. KIAA0090 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0090, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0090 BINDING SITE, designated SEQ ID:42651, to the nucleotide sequence of VGAM759 RNA, herein designated VGAM RNA, also designated SEQ ID:3470.

[29842] Another function of VGAM759 is therefore inhibition of KIAA0090 (Accession XM\_114045). Accordingly, utilities of VGAM759 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0090. LOC138199 (Accession XM\_059950) is another VGAM759 host target gene. LOC138199 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC138199, corresponding

to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC138199 BINDING SITE, designated SEQ ID:37117, to the nucleotide sequence of VGAM759 RNA, herein designated VGAM RNA, also designated SEQ ID:3470.

[29843] Another function of VGAM759 is therefore inhibition of LOC138199 (Accession XM\_059950). Accordingly, utilities of VGAM759 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC138199. LOC254228 (Accession XM\_171123) is another VGAM759 host target gene. LOC254228 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254228 BINDING SITE, designated SEQ ID:45916, to the nucleotide sequence of VGAM759 RNA, herein designated VGAM RNA, also designated SEQ ID:3470.

[29844] Another function of VGAM759 is therefore inhibition of LOC254228 (Accession XM\_171123). Accordingly, utilities of VGAM759 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC254228. LOC254251 (Accession XM\_171088) is another VGAM759 host target gene. LOC254251 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254251 BINDING SITE, designated SEQ ID:45900, to the nucleotide sequence of VGAM759 RNA, herein designated VGAM RNA, also designated SEQ ID:3470.

[29845] Another function of VGAM759 is therefore inhibition of LOC254251 (Accession XM\_171088). Accordingly, utilities of VGAM759 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254251. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 760 (VGAM760) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29846] VGAM760 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM760 was detected is described hereinabove with reference to Figs. 1–8.

[29847] VGAM760 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM760 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29848] VGAM760 gene encodes a VGAM760 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM760 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM760 precursor RNA is designated SEQ ID:746, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:746 is located at position 14942 relative to the genome of Bovine Coronavirus.

[29849] VGAM760 precursor RNA folds onto itself, forming VGAM760 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA



genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29850] An enzyme complex designated DICER COMPLEX, `dices` the VGAM760 folded precursor RNA into VGAM760 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM760 RNA is designated SEQ ID:3471, and is provided hereinbelow with reference to the sequence listing part.

[29851] VGAM760 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM760 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM760 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29852] VGAM760 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM760 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM760 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM760 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM760 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29853] The complementary binding of VGAM760 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM760 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM760 host target RNA into VGAM760 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29854] It is appreciated that VGAM760 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM760 host target genes. The mRNA of each one of this plurality of VGAM760 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM760 RNA, herein designated VGAM RNA, and which when bound by VGAM760 RNA causes inhibition of translation of respective one or more VGAM760 host target proteins.

[29855] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM760 gene, herein designated VGAM GENE, on one or more VGAM760 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29856] It is yet further appreciated that a function of VGAM760 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM760 correlate with, and may be deduced from, the identity of the host target genes which VGAM760 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29857] Nucleotide sequences of the VGAM760 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM760 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM760 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM760 are further described hereinbelow with reference to Table 1.

[29858] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM760 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM760 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29859] As mentioned hereinabove with reference to Fig. 1, a function of VGAM760 gene, herein designated VGAM is inhibition of expression of VGAM760 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM760 correlate with, and may be deduced from, the identity of the target genes which VGAM760 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29860] Erythrocyte Membrane Protein Band 4.9 (dematin) (EPB49, Accession NM\_001978) is a VGAM760 host target gene. EPB49 BINDING SITE is HOST TARGET binding site found in

the 3' untranslated region of mRNA encoded by EPB49, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPB49 BINDING SITE, designated SEQ ID:7710, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29861] A function of VGAM760 is therefore inhibition of Erythrocyte Membrane Protein Band 4.9 (dematin) (EPB49, Accession NM\_001978), a gene which is an actin-bundling protein. Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPB49. The function of EPB49 has been established by previous studies. Chishti et al. (1989) proposed the name dematin (from the Greek 'dema,' a bundle) for an actin-bundling protein originally identified in the human erythroid membrane skeleton. It consists of 2 polypeptide chains of 48 and 52 kD that have been identified as protein 4.9 on SDS/polyacrylamide gels. In solution, dematin exists as a trimer and bundles actin filaments in a phosphorylation-dependent manner. Its actin-bundling activity is abolished upon phosphorylation by cAMP-dependent protein kinase and is restored after

dephosphorylation. See review of Gilligan and Bennett (1993). Rana et al. (1993) reported the complete primary structure of human erythroid dematin, whose sequence includes a homolog of the 'headpiece' sequence found at the C-terminus of villin (OMIM Ref. No. 193040). The headpiece is essential for villin function in inducing microvillar development and actin redistribution. The widespread expression of dematin transcripts in human tissue suggests that dematin and its homologs may substitute for villin in villin-negative tissues to regulate actin reorganization by a phosphorylation-regulated mechanism. Peters et al. (1995) demonstrated that the murine dematin gene, symbolized Epb4.9, maps to chromosome 14. They raised the possibility that dematin mutations may be involved in neurologic abnormalities in the mouse. Although dematin is an actin-bundling protein of the erythroid membrane skeleton, it is abundantly expressed in human brain, heart, skeletal muscle, kidney, and lung. Azim et al. (1995) noted that the 48-kD subunit of dematin contains the headpiece domain of villin which is essential for its morphogenic function in vivo. Azim et al. (1995) reported the primary structure of the 52-kD subunit of dematin which differs from the 48-kD subunit by a

22-amino acid insertion within its headpiece domain. A unique feature of the insertion sequence of the 52-kD subunit is its homology to erythrocyte protein 4.2 (OMIM Ref. No. 177070). Using somatic cell hybrid panels and fluorescence in situ hybridization, Azim et al. (1995) localized the dematin gene to 8p21.1, a site distal to the locus of ankyrin (OMIM Ref. No. 182900) at 8p11.2. Azim et al. (1996) demonstrated that dematin and protein 4.2 (OMIM Ref. No. 177070) bind ATP. Although the functional significance is not clear, the findings open new perspectives for the function of these 2 proteins in vivo. By using homologous recombination in mouse embryonic stem cells, Khanna et al. (2002) deleted the headpiece domain of dematin to evaluate its function in vivo. Dematin headpiece-null mice were viable and born at the expected mendelian ratio. Hematologic evaluation showed evidence of compensated anemia and spherocytosis in these mice, however. The headpiece-null erythrocytes were osmotically fragile, and displayed reduced deformability and filterability. In vitro, significantly greater membrane fragmentation of these erythrocytes was demonstrated. Biochemical characterization showed a weakened membrane skeleton evidenced by reduced association of spectrin and



actin to the plasma membrane. Together, these results provided evidence for the physiologic significance of dematin and demonstrated a role for the headpiece domain in the maintenance of structural integrity and mechanical properties of red cells in vivo.

[29862] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[29863] Khanna, R.; Chang, S. H.; Andrabi, S.; Azam, M.; Kim, A.; Rivera, A.; Brugnara, C.; Low, P. S.; Liu, S.-C.; Chishti, A. H. : Headpiece domain of dematin is required for the stability of the erythrocyte membrane. *Proc. Nat. Acad. Sci.* 99: 6637–6642, 2002. ; and

[29864] Peters, L. L.; Eicher, E. M.; Azim, A. C.; Chishti, A. H. : The gene encoding the erythrocyte membrane skeleton protein dematin (Epb4.9) maps to mouse chromosome 14. *Genomics* 26: 634–63.

[29865] Further studies establishing the function and utilities of EPB49 are found in John Hopkins OMIM database record ID 125305, and in cited publications numbered 2664–2670 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Coagulation Factor II (thrombin) Receptor-like 3 (F2RL3, Accession

NM\_003950) is another VGAM760 host target gene. F2RL3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by F2RL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F2RL3 BINDING SITE, designated SEQ ID:10082, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29866] Another function of VGAM760 is therefore inhibition of Coagulation Factor II (thrombin) Receptor-like 3 (F2RL3, Accession NM\_003950), a gene which Protease-activated receptor 4; G protein-coupled receptor that increases phosphoinositide hydrolysis. Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F2RL3. The function of F2RL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM193.FLJ11029 (Accession XM\_027783) is another VGAM760 host target gene. FLJ11029 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ11029, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11029 BINDING SITE, designated SEQ ID:30569, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29867] Another function of VGAM760 is therefore inhibition of FLJ11029 (Accession XM\_027783). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11029. FLJ21168 (Accession NM\_025073) is another VGAM760 host target gene. FLJ21168 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21168, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21168 BINDING SITE, designated SEQ ID:24674, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29868] Another function of VGAM760 is therefore inhibition of FLJ21168 (Accession NM\_025073). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ21168. Guanine Nucleotide Binding Protein (G protein), Gamma 10 (GNG10, Accession NM\_004125) is another VGAM760 host target gene. GNG10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GNG10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GNG10 BINDING SITE, designated SEQ ID:10332, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29869] Another function of VGAM760 is therefore inhibition of Guanine Nucleotide Binding Protein (G protein), Gamma 10 (GNG10, Accession NM\_004125). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GNG10. GR6 (Accession NM\_007354) is another VGAM760 host target gene. GR6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GR6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of GR6 BINDING SITE, designated SEQ ID:14283, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29870] Another function of VGAM760 is therefore inhibition of GR6 (Accession NM\_007354). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GR6. HBOA (Accession NM\_007067) is another VGAM760 host target gene. HBOA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HBOA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HBOA BINDING SITE, designated SEQ ID:13931, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29871] Another function of VGAM760 is therefore inhibition of HBOA (Accession NM\_007067). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HBOA. KIAA0319 (Accession NM\_014809) is another VGAM760

host target gene. KIAA0319 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0319, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0319 BINDING SITE, designated SEQ ID:16766, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29872] Another function of VGAM760 is therefore inhibition of KIAA0319 (Accession NM\_014809). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0319. KIAA0472 (Accession XM\_050147) is another VGAM760 host target gene. KIAA0472 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0472, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0472 BINDING SITE, designated SEQ ID:35576, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29873] Another function of VGAM760 is therefore inhibition of KIAA0472 (Accession XM\_050147). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0472. PAS Domain Containing Serine/threonine Kinase (PASK, Accession NM\_015148) is another VGAM760 host target gene. PASK BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PASK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PASK BINDING SITE, designated SEQ ID:17502, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29874] Another function of VGAM760 is therefore inhibition of PAS Domain Containing Serine/threonine Kinase (PASK, Accession NM\_015148). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PASK. LOC220883 (Accession XM\_166076) is another VGAM760 host target gene. LOC220883 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by LOC220883, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220883 BINDING SITE, designated SEQ ID:43852, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29875] Another function of VGAM760 is therefore inhibition of LOC220883 (Accession XM\_166076). Accordingly, utilities of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220883. LOC221662 (Accession XM\_166466) is another VGAM760 host target gene. LOC221662 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221662, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221662 BINDING SITE, designated SEQ ID:44390, to the nucleotide sequence of VGAM760 RNA, herein designated VGAM RNA, also designated SEQ ID:3471.

[29876] Another function of VGAM760 is therefore inhibition of LOC221662 (Accession XM\_166466). Accordingly, utilities



of VGAM760 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221662. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 761 (VGAM761) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29877] VGAM761 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM761 was detected is described hereinabove with reference to Figs. 1–8.

[29878] VGAM761 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM761 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29879] VGAM761 gene encodes a VGAM761 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM761 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM761 precursor RNA is designated SEQ ID:747, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:747 is located at position 5511 relative to the genome of Bovine Coronavirus.

[29880] VGAM761 precursor RNA folds onto itself, forming VGAM761 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29881] An enzyme complex designated DICER COMPLEX, `dices` the VGAM761 folded precursor RNA into VGAM761 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 57%) nucleotide sequence of VGAM761 RNA is designated SEQ ID:3472, and

is provided hereinbelow with reference to the sequence listing part.

[29882] VGAM761 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM761 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM761 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29883] VGAM761 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM761 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM761 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM761 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM761 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29884] The complementary binding of VGAM761 RNA, herein designated VGAM RNA, to host target binding sites on VGAM761 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM761 host target RNA into VGAM761 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29885] It is appreciated that VGAM761 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM761 host target genes. The mRNA of each one of this plurality of VGAM761 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM761 RNA, herein designated VGAM RNA, and which when bound by VGAM761 RNA causes inhibition of translation of respective one or more VGAM761 host target proteins.

[29886] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM761 gene, herein designated VGAM GENE, on one or more VGAM761 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29887] It is yet further appreciated that a function of VGAM761 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM761 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM761 correlate with, and may be deduced from, the identity of the host target genes which VGAM761 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29888] Nucleotide sequences of the VGAM761 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM761 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM761 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM761 are further described hereinbelow with reference to Table 1.

[29889] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM761 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM761 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29890] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM761 gene, herein designated VGAM is inhibition of expression of VGAM761 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM761 correlate with, and may be deduced from, the identity of the target genes which VGAM761 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29891] GTP Binding Protein 5 (putative) (GTPBP5, Accession XM\_037206) is a VGAM761 host target gene. GTPBP5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GTPBP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GTPBP5 BINDING SITE, designated SEQ ID:32575, to the nucleotide sequence of VGAM761 RNA, herein designated VGAM RNA, also designated SEQ ID:3472.

[29892] A function of VGAM761 is therefore inhibition of GTP Binding Protein 5 (putative) (GTPBP5, Accession XM\_037206). Accordingly, utilities of VGAM761 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GTPBP5. KIAA0625 (Accession NM\_015046) is another VGAM761 host target

gene. KIAA0625 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA0625, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0625 BINDING SITE, designated SEQ ID:17407, to the nucleotide sequence of VGAM761 RNA, herein designated VGAM RNA, also designated SEQ ID:3472.

[29893] Another function of VGAM761 is therefore inhibition of KIAA0625 (Accession NM\_015046). Accordingly, utilities of VGAM761 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0625. KIAA1493 (Accession XM\_034415) is another VGAM761 host target gene. KIAA1493 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1493, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1493 BINDING SITE, designated SEQ ID:32087, to the nucleotide sequence of VGAM761 RNA, herein designated VGAM RNA, also designated SEQ ID:3472.



[29894] Another function of VGAM761 is therefore inhibition of KIAA1493 (Accession XM\_034415). Accordingly, utilities of VGAM761 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1493. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 762 (VGAM762) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29895] VGAM762 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM762 was detected is described hereinabove with reference to Figs. 1–8.

[29896] VGAM762 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM762 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29897] VGAM762 gene encodes a VGAM762 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM762

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM762 precursor RNA is designated SEQ ID:748, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:748 is located at position 3576 relative to the genome of Bovine Coronavirus.

[29898] VGAM762 precursor RNA folds onto itself, forming VGAM762 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29899] An enzyme complex designated DICER COMPLEX, `dices` the VGAM762 folded precursor RNA into VGAM762 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 53%) nucleotide sequence of VGAM762 RNA is designated SEQ ID:3473, and is provided hereinbelow with reference to the sequence listing part.

[29900] VGAM762 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM762 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM762 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[29901] VGAM762 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM762 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM762 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM762 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM762 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29902] The complementary binding of VGAM762 RNA, herein designated VGAM RNA, to host target binding sites on VGAM762 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM762 host target RNA into VGAM762 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29903] It is appreciated that VGAM762 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM762 host target genes. The mRNA of each one of this plurality of VGAM762 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM762 RNA, herein designated VGAM RNA, and which when bound by VGAM762 RNA causes inhibition of translation of respective one or more VGAM762 host target proteins.

[29904] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM762 gene, herein designated VGAM GENE, on one or more VGAM762 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29905] It is yet further appreciated that a function of VGAM762 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM762 correlate with, and may be deduced from, the identity of the host target genes which VGAM762 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29906] Nucleotide sequences of the VGAM762 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM762 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM762 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM762 are further described hereinbelow with reference to Table 1.

[29907] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM762 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM762 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[29908] As mentioned hereinabove with reference to Fig. 1, a function of VGAM762 gene, herein designated VGAM is inhibition of expression of VGAM762 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM762 correlate with, and may be deduced from, the identity of the target genes which VGAM762 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29909] Apolipoprotein B mRNA Editing Enzyme, Catalytic Polypeptide 1 (APOBEC1, Accession NM\_005889) is a VGAM762 host target gene. APOBEC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APOBEC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APOBEC1 BINDING SITE, designated SEQ ID:12510, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29910] A function of VGAM762 is therefore inhibition of Apolipoprotein B mRNA Editing Enzyme, Catalytic Polypeptide 1 (APOBEC1, Accession NM\_005889). Accord-

ingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOBEC1. Chloride Channel 4 (CLCN4, Accession NM\_001830) is another VGAM762 host target gene. CLCN4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLCN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLCN4 BINDING SITE, designated SEQ ID:7570, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29911] Another function of VGAM762 is therefore inhibition of Chloride Channel 4 (CLCN4, Accession NM\_001830), a gene which is regulation of cell volume; membrane potential stabilization, signal transduction and transepithelial transport. Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCN4. The function of CLCN4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to



VGAM558.Protocadherin Alpha 1 (PCDHA1, Accession NM\_018900) is another VGAM762 host target gene.

PCDHA1 BINDING SITE1 and PCDHA1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PCDHA1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA1 BINDING SITE1 and PCDHA1 BINDING SITE2, designated SEQ ID:20868 and SEQ ID:25387 respectively, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29912] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 1 (PCDHA1, Accession NM\_018900). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA1. Protocadherin Alpha 10 (PCDHA10, Accession NM\_031860) is another VGAM762 host target gene. PCDHA10 BINDING SITE1 and PCDHA10 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PCDHA10, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of PCDHA10 BINDING SITE1 and PCDHA10 BINDING SITE2, designated SEQ ID:25619 and SEQ ID:20889 respectively, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29913] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 10 (PCDHA10, Accession NM\_031860). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA10. Protocadherin Alpha 13 (PCDHA13, Accession NM\_018904) is another VGAM762 host target gene. PCDHA13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA13 BINDING SITE, designated SEQ ID:20909, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29914] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 13 (PCDHA13, Accession NM\_018904). Accordingly, utilities of VGAM762 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA13. Protocadherin Alpha 2 (PCDHA2, Accession NM\_018905) is another VGAM762 host target gene. PCDHA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA2 BINDING SITE, designated SEQ ID:20919, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29915] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 2 (PCDHA2, Accession NM\_018905). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA2. Protocadherin Alpha 3 (PCDHA3, Accession NM\_018906) is another VGAM762 host target gene. PCDHA3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of PCDHA3 BINDING SITE, designated SEQ ID:20929, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29916] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 3 (PCDHA3, Accession NM\_018906). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA3. Protocadherin Alpha 4 (PCDHA4, Accession NM\_018907) is another VGAM762 host target gene. PCDHA4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA4 BINDING SITE, designated SEQ ID:20939, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29917] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 4 (PCDHA4, Accession NM\_018907). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with PCDHA4. Protocadherin Alpha 5 (PCDHA5, Accession NM\_018908) is another VGAM762 host target gene. PCDHA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA5 BINDING SITE, designated SEQ ID:20949, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29918] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 5 (PCDHA5, Accession NM\_018908). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA5. Protocadherin Alpha 6 (PCDHA6, Accession NM\_018909) is another VGAM762 host target gene. PCDHA6 BINDING SITE1 and PCDHA6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PCDHA6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA6

BINDING SITE1 and PCDHA6 BINDING SITE2, designated SEQ ID:20959 and SEQ ID:25591 respectively, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29919] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 6 (PCDHA6, Accession NM\_018909). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA6. Protocadherin Alpha 8 (PCDHA8, Accession NM\_018911) is another VGAM762 host target gene. PCDHA8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA8 BINDING SITE, designated SEQ ID:20979, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29920] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 8 (PCDHA8, Accession NM\_018911). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with PCDHA8. Protocadherin Alpha 9 (PCDHA9, Accession NM\_031857) is another VGAM762 host target gene. PCDHA9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA9 BINDING SITE, designated SEQ ID:25605, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29921] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha 9 (PCDHA9, Accession NM\_031857), a gene which is a calcium-dependent cell-adhesion protein. Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA9. The function of PCDHA9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM71. Protocadherin Alpha Subfamily C, 1 (PCDHAC1, Accession NM\_018898) is another VGAM762 host target gene. PCDHAC1 BINDING SITE is HOST TARGET binding

site found in the 3` untranslated region of mRNA encoded by PCDHAC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHAC1 BINDING SITE, designated SEQ ID:20848, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29922] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha Subfamily C, 1 (PCDHAC1, Accession NM\_018898). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHAC1. Protocadherin Alpha Subfamily C, 2 (PCDHAC2, Accession NM\_018899) is another VGAM762 host target gene. PCDHAC2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PCDHAC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHAC2 BINDING SITE, designated SEQ ID:20858, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.



[29923] Another function of VGAM762 is therefore inhibition of Protocadherin Alpha Subfamily C, 2 (PCDHAC2, Accession NM\_018899). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHAC2. Calmodulin Binding Transcription Activator 1 (CAMTA1, Accession XM\_042323) is another VGAM762 host target gene. CAMTA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAMTA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAMTA1 BINDING SITE, designated SEQ ID:33718, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29924] Another function of VGAM762 is therefore inhibition of Calmodulin Binding Transcription Activator 1 (CAMTA1, Accession XM\_042323). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAMTA1. FLJ12121 (Accession NM\_024978) is another VGAM762 host target gene. FLJ12121 BINDING SITE is HOST TARGET binding

site found in the 3' untranslated region of mRNA encoded by FLJ12121, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12121 BINDING SITE, designated SEQ ID:24537, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29925] Another function of VGAM762 is therefore inhibition of FLJ12121 (Accession NM\_024978). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12121. KIAA0329 (Accession NM\_014844) is another VGAM762 host target gene. KIAA0329 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0329, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0329 BINDING SITE, designated SEQ ID:16876, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29926] Another function of VGAM762 is therefore inhibition of

KIAA0329 (Accession NM\_014844). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0329. KIAA0390 (Accession NM\_014717) is another VGAM762 host target gene. KIAA0390 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0390, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0390 BINDING SITE, designated SEQ ID:16269, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29927] Another function of VGAM762 is therefore inhibition of KIAA0390 (Accession NM\_014717). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0390. KIAA1550 (Accession XM\_039393) is another VGAM762 host target gene. KIAA1550 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1550, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1550 BINDING SITE, designated SEQ ID:33071, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29928] Another function of VGAM762 is therefore inhibition of KIAA1550 (Accession XM\_039393). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1550. Methyl-CpG Binding Domain Protein 2 (MBD2, Accession NM\_015832) is another VGAM762 host target gene. MBD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MBD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MBD2 BINDING SITE, designated SEQ ID:17946, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29929] Another function of VGAM762 is therefore inhibition of Methyl-CpG Binding Domain Protein 2 (MBD2, Accession NM\_015832). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBD2. Signaling Lympho-

cytic Activation Molecule (SLAM, Accession NM\_003037) is another VGAM762 host target gene. SLAM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLAM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLAM BINDING SITE, designated SEQ ID:8992, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29930] Another function of VGAM762 is therefore inhibition of Signaling Lymphocytic Activation Molecule (SLAM, Accession NM\_003037). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLAM. LOC118851 (Accession XM\_061180) is another VGAM762 host target gene. LOC118851 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC118851, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC118851 BINDING SITE, designated SEQ ID:37200, to the nucleotide sequence of

VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29931] Another function of VGAM762 is therefore inhibition of LOC118851 (Accession XM\_061180). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC118851. LOC146890 (Accession XM\_097128) is another VGAM762 host target gene. LOC146890 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146890, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146890 BINDING SITE, designated SEQ ID:40764, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29932] Another function of VGAM762 is therefore inhibition of LOC146890 (Accession XM\_097128). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146890. LOC157627 (Accession XM\_088347) is another VGAM762 host target gene. LOC157627 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC157627, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157627 BINDING SITE, designated SEQ ID:39621, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29933] Another function of VGAM762 is therefore inhibition of LOC157627 (Accession XM\_088347). Accordingly, utilities of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157627. LOC163682 (Accession XM\_099402) is another VGAM762 host target gene. LOC163682 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163682, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163682 BINDING SITE, designated SEQ ID:42093, to the nucleotide sequence of VGAM762 RNA, herein designated VGAM RNA, also designated SEQ ID:3473.

[29934] Another function of VGAM762 is therefore inhibition of LOC163682 (Accession XM\_099402). Accordingly, utilities

of VGAM762 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163682. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 763 (VGAM763) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29935] VGAM763 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM763 was detected is described hereinabove with reference to Figs. 1–8.

[29936] VGAM763 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM763 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29937] VGAM763 gene encodes a VGAM763 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM763 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–



quence of VGAM763 precursor RNA is designated SEQ ID:749, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:749 is located at position 18582 relative to the genome of Bovine Coronavirus.

[29938] VGAM763 precursor RNA folds onto itself, forming VGAM763 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29939] An enzyme complex designated DICER COMPLEX, `dices` the VGAM763 folded precursor RNA into VGAM763 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM763 RNA is designated SEQ ID:3474, and

is provided hereinbelow with reference to the sequence listing part.

[29940] VGAM763 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM763 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM763 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29941] VGAM763 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM763 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM763 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM763 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM763 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29942] The complementary binding of VGAM763 RNA, herein designated VGAM RNA, to host target binding sites on VGAM763 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM763 host target RNA into VGAM763 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29943] It is appreciated that VGAM763 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM763 host target genes. The mRNA of each one of this plurality of VGAM763 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM763 RNA, herein designated VGAM RNA, and which when bound by VGAM763 RNA causes inhibition of translation of respective one or more VGAM763 host target proteins.

[29944] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM763 gene, herein designated VGAM GENE, on one or more VGAM763 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29945] It is yet further appreciated that a function of VGAM763 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM763 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM763 correlate with, and may be deduced from, the identity of the host target genes which VGAM763 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29946] Nucleotide sequences of the VGAM763 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM763 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM763 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM763 are further described hereinbelow with reference to Table 1.

[29947] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM763 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM763 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29948] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM763 gene, herein designated VGAM is inhibition of expression of VGAM763 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM763 correlate with, and may be deduced from, the identity of the target genes which VGAM763 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29949] MCF.2 Cell Line Derived Transforming Sequence (MCF2, Accession NM\_005369) is a VGAM763 host target gene. MCF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MCF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MCF2 BINDING SITE, designated SEQ ID:11840, to the nucleotide sequence of VGAM763 RNA, herein designated VGAM RNA, also designated SEQ ID:3474.

[29950] A function of VGAM763 is therefore inhibition of MCF.2 Cell Line Derived Transforming Sequence (MCF2, Accession NM\_005369), a gene which Cytoplasmic oncoprotein similar to vimentin. Accordingly, utilities of VGAM763 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MCF2. The function of

MCF2 has been established by previous studies. MCF2 is the designation of a transforming sequence identified using cotransfection of DNA from a human mammary carcinoma cell line. Noguchi et al. (1987) cloned this sequence and found that it did not cross-hybridize with the known oncogenes tested. By in situ hybridization, Noguchi et al. (1987) localized it to Xq27. This localization was confirmed by hybridization to DNA from a panel of human-rodent somatic cell hybrid lines. By pulsed field gel electrophoresis, Nguyen et al. (1987) found that the MCF2 gene and the F9 gene (OMIM Ref. No. 306900) are separated by a maximum distance of about 270 kb. Furthermore, they located several HTF islands in this region, i.e., CpG-rich, unmethylated sequences, containing several sites for 'rare cutter' enzymes, which are believed to be associated with expressed 'housekeeping' genes. Anson et al. (1988) further narrowed the interval separating MCF2 and F9, locating MCF2 to a region between 29 and 61 kb 3-prime to F9. In 2 unrelated hemophilia B (OMIM Ref. No. 306900) patients who raised antibodies to infused factor IX, they found deletions in excess of 273 kb encompassing the F9 and MCF2 genes and a CG-rich island. This appears to have been the first reported nullisomic deletion

of a transforming gene. No clinical condition could be attributed to the loss of the MCF2 gene. The CG-rich island may be a marker for an as yet undefined gene lying just 5-prime or just 3-prime off the island. Nguyen et al. (1989) concluded from pulsed field gel electrophoresis studies of the Xq27 region that MCF2 is located telomeric to F9. Grant et al. (1990) demonstrated that Mcf-2 in the mouse lies in the same order as the corresponding gene on the human X chromosome: Hprt--Cf-9--Mcf-2--G6pd. In situ hybridization indicated that the gene lies in the same region as Cf-9 and linkage studies in interspecific mouse backcross populations demonstrated that the Cf-9 and Mcf-2 genes were separated by about 0.5 cM. A comparison of the restriction maps of the DBL and MCF2 oncogenes, together with their chromosomal localization, indicates that they represent the same genetic locus. The DBL oncogene was initially detected as a transforming gene from a human diffuse B-cell lymphoma and was isolated as a 45-kb transforming human DNA sequence by cosmid cloning (Eva and Aaronson, 1985). By molecular hybridization, DBL lacks detectable homology with a large number of cellular or retroviral oncogenes, including members of the tyrosine kinase



family. Srivastava et al. (1986) demonstrated that anti-serum from mice bearing tumors induced by this onco-gene specifically detected a protein of about 66 kD in DBL transformants. Using DBL cDNA, they isolated mRNA from a transfectant clone and found that it directed the in vitro synthesis of this protein. Subcellular localization studies showed that the protein, also known as p66, is a cytoplasmic protein distributed between cytosol and crude membrane fractions. They showed, furthermore, that p66 is a phosphoprotein, with phosphorylation specific to serine residues. Ron et al. (1988) showed that overexpression of DBL is sufficient to transform NIH 3T3 cells. Ron et al. (1988) cloned and characterized the DBL oncogene. The DBL oncogene was generated by rearrangements involving 3 discontinuous regions of the human genome. By analysis of DNA from human/rodent somatic cell hybrids, Tronick et al. (1989) demonstrated that the DBL gene located on the X chromosome underwent recombination at its 5-prime and 3-prime ends with sequences derived from chromosomes 3 (pter-p21) and 16 (p13-q22), respectively. By in situ hybridization, Tronick et al. (1989) located the DBL gene more precisely to Xq27. Oncogenic activation of the MCF2 gene occurs through substitution

of part of its 5-prime coding region by unrelated nonsyn-  
tenic sequences. Galland et al. (1992) demonstrated that  
the upstream replacing sequence, referred to as URS, rep-  
resents the farthest 5-prime portion of the locus and that  
it is derived from the D15S93 locus on human chromo-  
some 15q15-q23.

[29951] Full details of the abovementioned studies are described  
in the following publications, the disclosure of which are  
hereby incorporated by reference:

[29952] Grant, S. G.; Mattei, M.-G.; Galland, F.; Stephenson, D. A.;  
Keitz, B. T.; Birnbaum, D.; Chapman, V. M. : Localization  
of the mouse Mcf-2 (Dbl) protooncogene within a con-  
served linkage group on the mouse X chromosome. Cyto-  
genet. Cell Genet. 54: 175-181, 1990. ; and

[29953] Anson, D. S.; Blake, D. J.; Winship, P. R.; Birnbaum, D.;  
Brownlee, G. G. : Nullisomic deletion of the mcf.2 trans-  
forming gene in two haemophilia B patients. EMBO J. 7:  
2795-2799, 1988.

[29954] Further studies establishing the function and utilities of  
MCF2 are found in John Hopkins OMIM database record ID  
311030, and in cited publications numbered 1139 and  
8618-8626 listed in the bibliography section hereinbelow,  
which are also hereby incorporated by refer-

ence.KIAA0293 (Accession XM\_027045) is another VGAM763 host target gene. KIAA0293 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0293, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0293 BINDING SITE, designated SEQ ID:30392, to the nucleotide sequence of VGAM763 RNA, herein designated VGAM RNA, also designated SEQ ID:3474.

[29955] Another function of VGAM763 is therefore inhibition of KIAA0293 (Accession XM\_027045). Accordingly, utilities of VGAM763 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0293. LOC91664 (Accession XM\_039908) is another VGAM763 host target gene. LOC91664 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC91664, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91664 BINDING SITE, designated SEQ ID:33211, to the nucleotide sequence of VGAM763 RNA, herein designated

VGAM RNA, also designated SEQ ID:3474.

[29956] Another function of VGAM763 is therefore inhibition of LOC91664 (Accession XM\_039908). Accordingly, utilities of VGAM763 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91664. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 764 (VGAM764) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29957] VGAM764 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM764 was detected is described hereinabove with reference to Figs. 1–8.

[29958] VGAM764 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM764 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29959] VGAM764 gene encodes a VGAM764 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM764 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM764 precursor RNA is designated SEQ ID:750, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:750 is located at position 11280 relative to the genome of Bovine Coronavirus.

[29960] VGAM764 precursor RNA folds onto itself, forming VGAM764 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29961] An enzyme complex designated DICER COMPLEX, `dices` the VGAM764 folded precursor RNA into VGAM764 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 51%) nucleotide sequence of VGAM764 RNA is designated SEQ ID:3475, and is provided hereinbelow with reference to the sequence listing part.

[29962] VGAM764 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM764 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM764 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[29963] VGAM764 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM764 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM764 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM764 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM764 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[29964] The complementary binding of VGAM764 RNA, herein designated VGAM RNA, to host target binding sites on VGAM764 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM764 host target RNA into VGAM764 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29965] It is appreciated that VGAM764 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM764 host target genes. The mRNA of

each one of this plurality of VGAM764 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM764 RNA, herein designated VGAM RNA, and which when bound by VGAM764 RNA causes inhibition of translation of respective one or more VGAM764 host target proteins.

[29966] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM764 gene, herein designated VGAM GENE, on one or more VGAM764 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science



294,779 (2001)).

[29967] It is yet further appreciated that a function of VGAM764 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM764 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM764 correlate with, and may be deduced from, the identity of the host target genes which VGAM764 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29968] Nucleotide sequences of the VGAM764 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM764 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM764 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM764 are further described hereinbelow with reference to Table 1.

[29969] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM764 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM764 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[29970] As mentioned hereinabove with reference to Fig. 1, a function of VGAM764 gene, herein designated VGAM is inhibition of expression of VGAM764 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM764 correlate with, and may be deduced from, the identity of the target genes which VGAM764 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29971] Chromosome 21 Open Reading Frame 25 (C21orf25, Accession XM\_032945) is a VGAM764 host target gene. C21orf25 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C21orf25, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C21orf25 BINDING SITE, designated SEQ ID:31794, to the nucleotide sequence of VGAM764 RNA, herein designated VGAM RNA, also designated SEQ ID:3475.

[29972] A function of VGAM764 is therefore inhibition of Chromosome 21 Open Reading Frame 25 (C21orf25, Accession

XM\_032945). Accordingly, utilities of VGAM764 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C21orf25. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 765 (VGAM765) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29973] VGAM765 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM765 was detected is described hereinabove with reference to Figs. 1–8.

[29974] VGAM765 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM765 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29975] VGAM765 gene encodes a VGAM765 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM765 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM765 precursor RNA is designated SEQ ID:751, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:751 is located at position 8100 relative to the genome of Bovine Coronavirus.

[29976] VGAM765 precursor RNA folds onto itself, forming VGAM765 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29977] An enzyme complex designated DICER COMPLEX, `dices` the VGAM765 folded precursor RNA into VGAM765 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM765 RNA is designated SEQ ID:3476, and

is provided hereinbelow with reference to the sequence listing part.

[29978] VGAM765 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM765 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM765 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[29979] VGAM765 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM765 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM765 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM765 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM765 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29980] The complementary binding of VGAM765 RNA, herein designated VGAM RNA, to host target binding sites on VGAM765 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM765 host target RNA into VGAM765 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[29981] It is appreciated that VGAM765 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM765 host target genes. The mRNA of each one of this plurality of VGAM765 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM765 RNA, herein designated VGAM RNA, and which when bound by VGAM765 RNA causes inhibition of translation of respective one or more VGAM765 host target proteins.

[29982] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM765 gene, herein designated VGAM GENE, on one or more VGAM765 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[29983] It is yet further appreciated that a function of VGAM765 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM765 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM765 correlate with, and may be deduced from, the identity of the host target genes which VGAM765 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[29984] Nucleotide sequences of the VGAM765 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM765 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM765 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM765 are further described hereinbelow with reference to Table 1.

[29985] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM765 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM765 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[29986] As mentioned hereinabove with reference to Fig. 1, a



function of VGAM765 gene, herein designated VGAM is inhibition of expression of VGAM765 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM765 correlate with, and may be deduced from, the identity of the target genes which VGAM765 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[29987] Potassium Inwardly-rectifying Channel, Subfamily J, Member 16 (KCNJ16, Accession NM\_018658) is a VGAM765 host target gene. KCNJ16 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNJ16, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNJ16 BINDING SITE, designated SEQ ID:20727, to the nucleotide sequence of VGAM765 RNA, herein designated VGAM RNA, also designated SEQ ID:3476.

[29988] A function of VGAM765 is therefore inhibition of Potassium Inwardly-rectifying Channel, Subfamily J, Member 16 (KCNJ16, Accession NM\_018658). Accordingly, utilities of VGAM765 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNJ16.

CG005 (Accession NM\_014887) is another VGAM765 host target gene. CG005 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CG005, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CG005 BINDING SITE, designated SEQ ID:17038, to the nucleotide sequence of VGAM765 RNA, herein designated VGAM RNA, also designated SEQ ID:3476.

[29989] Another function of VGAM765 is therefore inhibition of CG005 (Accession NM\_014887). Accordingly, utilities of VGAM765 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CG005. LOC219401 (Accession XM\_166706) is another VGAM765 host target gene. LOC219401 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219401, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219401 BINDING SITE, designated SEQ ID:44584, to the nucleotide sequence of VGAM765 RNA, herein designated VGAM RNA,

also designated SEQ ID:3476.

[29990] Another function of VGAM765 is therefore inhibition of LOC219401 (Accession XM\_166706). Accordingly, utilities of VGAM765 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219401. LOC90462 (Accession XM\_031852) is another VGAM765 host target gene. LOC90462 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90462, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90462 BINDING SITE, designated SEQ ID:31503, to the nucleotide sequence of VGAM765 RNA, herein designated VGAM RNA, also designated SEQ ID:3476.

[29991] Another function of VGAM765 is therefore inhibition of LOC90462 (Accession XM\_031852). Accordingly, utilities of VGAM765 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90462. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 766 (VGAM766) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[29992] VGAM766 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM766 was detected is described hereinabove with reference to Figs. 1–8.

[29993] VGAM766 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM766 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[29994] VGAM766 gene encodes a VGAM766 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM766 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM766 precursor RNA is designated SEQ ID:752, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:752 is located at position 8663 relative to the genome of Bovine Coronavirus.

[29995] VGAM766 precursor RNA folds onto itself, forming

VGAM766 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[29996] An enzyme complex designated DICER COMPLEX, `dices` the VGAM766 folded precursor RNA into VGAM766 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM766 RNA is designated SEQ ID:3477, and is provided hereinbelow with reference to the sequence listing part.

[29997] VGAM766 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM766 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM766 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[29998] VGAM766 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM766 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM766 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM766 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM766 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[29999] The complementary binding of VGAM766 RNA, herein designated VGAM RNA, to host target binding sites on VGAM766 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM766 host target RNA into VGAM766 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30000] It is appreciated that VGAM766 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM766 host target genes. The mRNA of each one of this plurality of VGAM766 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM766 RNA, herein designated VGAM RNA, and which when bound by VGAM766 RNA causes inhibition of translation of respective one or more VGAM766 host target proteins.

[30001] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM766 gene, herein designated VGAM GENE, on one or more VGAM766 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30002] It is yet further appreciated that a function of VGAM766 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM766 correlate with, and may be deduced from, the identity of the host target genes which VGAM766 binds and inhibits, and the



function of these host target genes, as elaborated herein–below.

[30003] Nucleotide sequences of the VGAM766 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM766 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM766 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM766 are further described hereinbelow with reference to Table 1.

[30004] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM766 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM766 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30005] As mentioned hereinabove with reference to Fig. 1, a function of VGAM766 gene, herein designated VGAM is inhibition of expression of VGAM766 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM766 correlate with, and may be deduced from, the identity of the target genes which VGAM766 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[30006] Adenylate Kinase 1 (AK1, Accession NM\_000476) is a VGAM766 host target gene. AK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AK1 BINDING SITE, designated SEQ ID:6087, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30007] A function of VGAM766 is therefore inhibition of Adenylate Kinase 1 (AK1, Accession NM\_000476). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AK1. DMC1 Dosage Suppressor of Mck1 Homolog, Meiosis-specific Homologous Recombination (yeast) (DMC1, Accession NM\_007068) is another VGAM766 host target gene. DMC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DMC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of DMC1 BINDING SITE, designated SEQ ID:13933, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30008] Another function of VGAM766 is therefore inhibition of DMC1 Dosage Suppressor of Mck1 Homolog, Meiosis-specific Homologous Recombination (yeast) (DMC1, Accession NM\_007068). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DMC1. DXYS155E (Accession NM\_005088) is another VGAM766 host target gene. DXYS155E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DXYS155E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DXYS155E BINDING SITE, designated SEQ ID:11540, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30009] Another function of VGAM766 is therefore inhibition of DXYS155E (Accession NM\_005088), a gene which may be involved in b-cell activation. may also be involved in sig-

nal transduction and gene regulation. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DXYS155E. The function of DXYS155E has been established by previous studies. In the 2.6-megabase segment of the distal short arms of the X and Y chromosomes, called the pseudoautosomal region, Ellison et al. (1992) identified an expressed gene designated XE7. (See also 465000.) They reported the structure of the XE7 gene and its expression in various human tissues. The analysis of genomic and cDNA clones showed that alternative RNA splicing results in the production of 2 protein isoforms, one containing 385 amino acids and the other containing 695 residues. The smaller polypeptide is a truncated version of the larger and results from the inclusion of a cassette exon that has an in-frame stop codon. The XE7 gene appears to be ubiquitously expressed, and the production of both protein isoforms was predicted in each of the several tissues examined.

[30010] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30011] Ellison, J.; Passage, M.; Yu, L.-C.; Yen, P.; Mohandas, T. K.;

Shapiro, L. : Directed isolation of human genes that escape X inactivation. *Somat. Cell Molec. Genet.* 18: 259–268, 1992. ; and

[30012] Ellison, J. W.; Ramos, C.; Yen, P. H.; Shapiro, L. J. : Structure and expression of the human pseudoautosomal gene XE7. *Hum. Molec. Genet.* 1: 691–696, 1992.

[30013] Further studies establishing the function and utilities of DXYS155E are found in John Hopkins OMIM database record ID 312095, and in cited publications numbered 2916–2917 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fibronectin Leucine Rich Transmembrane Protein 2 (FLRT2, Accession NM\_013231) is another VGAM766 host target gene. FLRT2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLRT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLRT2 BINDING SITE, designated SEQ ID:14875, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30014] Another function of VGAM766 is therefore inhibition of Fi–

bronectin Leucine Rich Transmembrane Protein 2 (FLRT2, Accession NM\_013231), a gene which may have a function in cell adhesion and/or receptor signaling. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLRT2. The function of FLRT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. Histamine Receptor H1 (HRH1, Accession NM\_000861) is another VGAM766 host target gene. HRH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HRH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HRH1 BINDING SITE, designated SEQ ID:6525, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30015] Another function of VGAM766 is therefore inhibition of Histamine Receptor H1 (HRH1, Accession NM\_000861), a gene which stimulates the synthesis of inositol phosphate. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with HRH1. The function of HRH1 has been established by previous studies. Histamine is a ubiquitous messenger molecule released from mast cells, enterochromaffin-like cells, and neurons. Its various actions are mediated by 3 pharmacologically defined receptors termed the H1, H2 (OMIM Ref. No. 142703), and H3 (OMIM Ref. No. 604525) receptors. The H1 receptor was the first member of this family to be pharmacologically defined with the design of selective antagonists, the 'anti-histamines,' which are used to treat allergic and inflammatory reactions. The H1 receptor is expressed by various peripheral tissues, such as smooth muscle, and by neurons in the brain, where histamine may be involved in the control of wakefulness, mood, and hormone secretion. Yamashita et al. (1991) cloned a bovine H1 receptor cDNA and established its nucleotide sequence. Its homology with the corresponding sequence of other receptors confirmed that it belongs to the superfamily of receptors coupled with G proteins with 7 putative transmembrane domains. In addition to their expression in neuronal, gastric, and muscular tissue, the G protein-coupled receptors HRH1 and HRH2 are also expressed on T-helper lymphocytes and trigger different intracellular events upon acti-

vation. Using flow cytometric analysis, Jutel et al. (2001) demonstrated that histamine binds more strongly to Th1 than to Th2 cells. Flow cytometry and RT-PCR analysis showed that HRH1 is predominantly expressed on Th1 cells in an IL3 (OMIM Ref. No. 147740)–upregulatable manner, while HRH2 is predominant on Th2 cells. Stimulation of naive, CD45RA+ (see OMIM Ref. No. 151460) T cells with IL12 (OMIM Ref. No. 161560) resulted in preferential expression of HRH1, but stimulation with IL4 (OMIM Ref. No. 147780) resulted in suppressed expression of HRH1, demonstrating that mature CD45RO+ Th1 and Th2 lymphocytes preferentially but not exclusively express HRH1 and HRH2, and that HRH1 and HRH2 are regulated by cytokines present in the immune environment. Histamine stimulation of Th1 cells resulted in significant calcium flux that could be blocked by an HRH1 antagonist, while stimulation of Th2 cells led to cAMP formation that could be blocked by an HRH2, but not an HRH1, antagonist. Furthermore, histamine enhanced Th1 but inhibited Th2 responses to anti-CD3. Histamine also enhanced peripheral blood mononuclear cell responses in sensitized individuals to a predominantly Th1 antigen, but suppressed responses to Th2 allergens. Animal model exper–



iments lend further support to the function of HRH1. Ma et al. (2002) noted that pertussis toxin (PTX) elicits a range of responses in mice, including sensitization to vasoactive amines (VAAS) and increased vascular permeability subsequent to PTX-induced changes in vascular endothelial cells. Susceptible mouse strains die from hypotensive and hypovolemic shock on vasoactive amine challenge, whereas resistant strains do not. This hypersensitivity is controlled by an autosomal dominant locus, designated Bphs, localized to mouse chromosome 6. Using positional cloning, Ma et al. (2002) linked the Bphs locus to Hrh1. Mice lacking Hrh1 were protected from VAAS hypersensitivity, as well as from experimental allergic encephalomyelitis and experimental autoimmune orchitis. Sequence analysis showed that leu263-to-pro (L263P), met313-to-val (M313V), and ser331-to-pro (S331P) polymorphisms were associated with resistance to vasoactive amine challenge. The authors concluded that these Hrh1 alleles control both the autoimmune T-cell and vascular responses regulated by histamine after PTX sensitization.

[30016] It is appreciated that the abovementioned animal model for HRH1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appre-

ciated from the publications sited hereinbelow.

[30017] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30018] Jutel, M.; Watanabe, T.; Klunker, S.; Akdis, M.; Thomet, O. A. R.; Malolepszy, J.; Zak-Nejmark, T.; Koga, R.; Kobayashi, T.; Blaser, K.; Akdis, C. A. : Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. Nature 413: 420-425, 2001. ; and

[30019] Ma, R. Z.; Gao, J.; Meeker, N. D.; Fillmore, P. D.; Tung, K. S. K.; Watanabe, T.; Zachary, J. F.; Offner, H.; Blankenhorn, E. P.; Teuscher, C. : Identification of Bphs, an autoimmune di.

[30020] Further studies establishing the function and utilities of HRH1 are found in John Hopkins OMIM database record ID 600167, and in sited publications numbered 790 and 7906-7908 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Hormonally Upregulated Neu-associated Kinase (HUNK, Accession NM\_014586) is another VGAM766 host target gene. HUNK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by HUNK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HUNK BINDING SITE, designated SEQ ID:15950, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30021] Another function of VGAM766 is therefore inhibition of Hormonally Upregulated Neu-associated Kinase (HUNK, Accession NM\_014586). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUNK. Potassium Inwardly-rectifying Channel, Subfamily J, Member 5 (KCNJ5, Accession NM\_000890) is another VGAM766 host target gene. KCNJ5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNJ5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNJ5 BINDING SITE, designated SEQ ID:6588, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30022] Another function of VGAM766 is therefore inhibition of Potassium Inwardly-rectifying Channel, Subfamily J, Member 5 (KCNJ5, Accession NM\_000890), a gene which is a potassium inwardly-rectifying channel. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNJ5. The function of KCNJ5 has been established by previous studies. Potassium channels inhibited by cytosolic ATP are found in a wide variety of tissues. Tucker et al. (1995) noted that in the pancreatic beta-cell, potassium channels play a critical role in the regulation of insulin secretion, and in smooth muscle they are responsible for hypoxic vasodilatation. Moreover, these channels are the targets for several important classes of therapeutic drugs, including the antidiabetic sulfonamides and the antihypertensive potassium channel openers. In the heart, as in other tissues, K(ATP) channels are thought to couple the membrane potential to the metabolic status of the cell, and these normally quiescent channels are activated during transient ischemic and hypoxic periods when they contribute to shortening of the cardiac action potential duration. Ashford et al. (1994) cloned the rat heart K(ATP) channel, thus enabling the isolation of the human ho-

molog. The primary structure of KATP1 placed it in the J subfamily of inwardly rectifying potassium channels (Bond et al., 1994), such as KCNJ2 (OMIM Ref. No. 600681) and KCNJ4 (OMIM Ref. No. 600504); thus, the human homolog was designated KCNJ5. Wickman et al. (1997) reported a partial sequence of human GIRK4. They used human/rodent somatic cell hybrids to localize the human gene to chromosome 11, consistent with previous studies that localized the gene to 11q23-ter. Wickman et al. (1997) cloned the mouse Girk4 gene. They showed that the gene is expressed almost exclusively in the mouse heart. Using interspecific backcross analysis, Wickman et al. (1997) mapped the mouse Girk4 gene to chromosome 9, consistent with the mapping to human chromosome 11.

[30023] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30024] Ashford, M. L. J.; Bond, C. T.; Blair, T. A.; Adelman, J. P. : Cloning and functional expression of a rat heart KATP channel. *Nature* 370: 456-459, 1994. ; and

[30025] Bond, C. T.; Pessia, M.; Xia, X.-M.; Lagrutta, A.; Kavanaugh, M. P.; Adelman, J. P. : Cloning and expression of a family of inward rectifier potassium channels. *Receptors*

Channels 2: 183.

[30026] Further studies establishing the function and utilities of KCNJ5 are found in John Hopkins OMIM database record ID 600734, and in cited publications numbered 7511–7514 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Leptin (obesity homolog, mouse) (LEP, Accession NM\_000230) is another VGAM766 host target gene. LEP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LEP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LEP BINDING SITE, designated SEQ ID:5738, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30027] Another function of VGAM766 is therefore inhibition of Leptin (obesity homolog, mouse) (LEP, Accession NM\_000230). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LEP. Nucleoporin 62kDa (NUP62, Accession NM\_016553) is another VGAM766 host target gene. NUP62 BINDING SITE is HOST TARGET binding

site found in the 3` untranslated region of mRNA encoded by NUP62, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUP62 BINDING SITE, designated SEQ ID:18628, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30028] Another function of VGAM766 is therefore inhibition of Nucleoporin 62kDa (NUP62, Accession NM\_016553). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUP62. Pim-1 Oncogene (PIM1, Accession XM\_165800) is another VGAM766 host target gene. PIM1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PIM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIM1 BINDING SITE, designated SEQ ID:43754, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30029] Another function of VGAM766 is therefore inhibition of

Pim-1 Oncogene (PIM1, Accession XM\_165800), a gene which is a protooncogene. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIM1. The function of PIM1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM95. Src Family Associated Phosphoprotein 2 (SCAP2, Accession NM\_003930) is another VGAM766 host target gene. SCAP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCAP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCAP2 BINDING SITE, designated SEQ ID:10029, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30030] Another function of VGAM766 is therefore inhibition of Src Family Associated Phosphoprotein 2 (SCAP2, Accession NM\_003930), a gene which interacts with Src family protein tyrosine kinases and SLAP/FYB (SLA). Accordingly, utilities of VGAM766 include diagnosis, prevention and



treatment of diseases and clinical conditions associated with SCAP2. The function of SCAP2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM134. Solute Carrier Family 17 (anion/sugar transporter), Member 5 (SLC17A5, Accession NM\_012434) is another VGAM766 host target gene. SLC17A5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC17A5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC17A5 BINDING SITE, designated SEQ ID:14814, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30031] Another function of VGAM766 is therefore inhibition of Solute Carrier Family 17 (anion/sugar transporter), Member 5 (SLC17A5, Accession NM\_012434), a gene which is a member of a family of anion/cation symporters. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC17A5. The function of SLC17A5 has been es-

established by previous studies. Aula et al. (2000) identified a large number of mutations in SLC17A5 in patients presenting with either Salla disease or the infantile sialic acid storage disorder. All 80 Finnish patients with Salla disease had the R39C mutation (604322.0001); 91% of them were homozygous for this old founder mutation. The compound heterozygous patients, with the founder mutation in only 1 allele, presented with a more severe phenotype than did the homozygous patients. The same R39C mutation was also found in most of the Swedish patients with SD and in heterozygous form in 5 patients from central Europe who presented with an unusually severe (intermediate) SD phenotype. Ten different mutations, including deletions, insertions, and missense and nonsense mutations, were identified in patients with the most severe ISSD phenotype. Using a positional cloning approach in a search for the gene that is mutant in sialic acid storage diseases (see OMIM Ref. No. 269920), Verheijen et al. (1999) identified an EST from the region of mapping on 6q14–q15 that they labeled SLC17A5 and subsequently showed to be mutant in these disorders. The sequence they isolated included an open reading frame (ORF) of 1,485 bp, predicting a protein sequence of 495 amino

acids. A database search showed that the new sequence had homology to members of the anion/cation symporter (ACS) family of transporters. This family contains eukaryotic inorganic anion transporters (such as Na<sup>+</sup>/phosphate cotransporters) as well as prokaryotic organic anion transporters (including H<sup>+</sup>/acid sugar symporters for hexuronate and glucarate). Verheijen et al. (1999) suggested that the product of the SLC17A5 gene be designated 'sialin' because of its relation to sialic acid storage diseases. Sialin contains a characteristic motif in the fourth transmembrane-spanning domain that is present in all members of the ACS family. They could demonstrate homology of sialin with human Na<sup>+</sup>/phosphate symporters by sequence alignment. For example, sialin shows 34% sequence identity with NPT1 (SLC17A1; 182308). Only the N- and C-terminal regions do not show homology. Verheijen et al. (1999) found extensive homology of human sialin with proteins in other species. On Northern blot analysis of human tissues, Verheijen et al. (1999) found ubiquitous expression of an approximately 4.5-kb major transcript of SLC17A5, and an additional transcript of approximately 3.5 kb. They also observed a ubiquitously expressed 1.8-kb band after very long exposures. They sus-

pected that these different transcripts are due to multiple poly(A) addition sites. The SLC17A5 gene is also known as AST. Biancheri et al. (2002) described 2 Italian brothers with sialic acid storage disease that resembled Salla disease as observed in the Finnish population (OMIM Ref. No. 604369) rather than ISSD. Both brothers showed moderate intellectual disability, spastic ataxic syndrome, hypomyelination and cerebellar ataxia on MRI, and lysosomal storage, all typical of Salla disease. In one of the alleles of the younger brother, Biancheri et al. (2002) found the same 15-bp deletion in exon 6 that had been found by Verheijen et al. (1999). No R39C mutation (604322.0001) was found. The older brother had died at the age of 20 years and DNA testing was not performed. The second mutation in the younger brother was presumed to lie in a noncoding area of the gene.

[30032] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30033] Aula, N.; Salomaki, P.; Timonen, R.; Verheijen, F.; Mancini, G.; Mansson, J.-E.; Aula, P.; Peltonen, L. : The spectrum of SLC17A5-gene mutations resulting in free sialic acid-storage diseases indicates some genotype-phenotype

correlation. Am. J. Hum. Genet. 67: 832–840, 2000. ; and

[30034] Verheijen, F. W.; Verbeek, E.; Aula, N.; Beerens, C. E. M. T.; Havelaar, A. C.; Joosse, M.; Peltonen, L.; Aula, P.; Galjaard, H.; van der Spek, P. J.; Mancini, G. M. S. : A new gene.

[30035] Further studies establishing the function and utilities of SLC17A5 are found in John Hopkins OMIM database record ID 604322, and in cited publications numbered 5011, 10827, 10828–1082 and 1656–1661 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Sulfotransferase Family, Cytosolic, 2A, Dehydroepiandrosterone (DHEA) –preferring, Member 1 (SULT2A1, Accession XM\_049895) is another VGAM766 host target gene. SULT2A1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SULT2A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SULT2A1 BINDING SITE, designated SEQ ID:35540, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30036] Another function of VGAM766 is therefore inhibition of Sulfotransferase Family, Cytosolic, 2A, Dehydroepiandros–

terone (DHEA) –preferring, Member 1 (SULT2A1, Accession XM\_049895), a gene which catalyzes the sulfation of steroids and bile acids in the liver and adrenal glands. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SULT2A1. The function of SULT2A1 has been established by previous studies. One of the major roles of the sulfotransferases (ST) in the metabolism of drugs and endogenous compounds is the conversion of these substances into more hydrophilic water-soluble sulfate conjugates that can be easily excreted. Sulfation may also play a regulatory role for many endogenous compounds, such as steroids and neurotransmitters, by altering the biologic properties of these compounds. Otterness et al. (1992), Kong et al. (1992), and Comer et al. (1993) reported the cloning of cDNAs encoding liver dehydroepiandrosterone (DHEA) sulfotransferase. The predicted protein has 285 amino acids. Although Northern blot analysis of human liver RNA detected transcripts of 3 different sizes, Southern blot analysis of human DNA suggested that only 1 gene is present in the genome. This gene has an important role in the sulfation of both bile acids and steroids in the liver and adrenals. The human

adrenal form of this enzyme is physically, immunologically, and kinetically similar, perhaps identical, to the liver form. Dehydroepiandrosterone sulfate is quantitatively one of the major steroids secreted from the adrenal cortex. Since 20 to 25% of subjects have a high level of hepatic DHEA sulfotransferase activity, the possibility that this enzyme activity may be controlled by a genetic polymorphism was raised. Otterness et al. (1995) cloned the STD gene and demonstrated that it spans at least 17 kb and is composed of 6 exons and 5 introns.

[30037] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30038] Comer, K. A.; Falany, J. L.; Falany, C. N. : Cloning and expression of human liver dehydroepiandrosterone sulphotransferase. *Biochem. J.* 289: 233–240, 1993. ; and

[30039] Otterness, D. M.; Her, C.; Aksoy, S.; Kimura, S.; Wieben, E. D.; Weinshilboum, R. M. : Human dehydroepiandrosterone sulfotransferase gene: molecular cloning and structural characterizat.

[30040] Further studies establishing the function and utilities of SULT2A1 are found in John Hopkins OMIM database record ID 125263, and in sited publications numbered

1999–2004 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SUV39H2 (Accession NM\_024670) is another VGAM766 host target gene. SUV39H2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SUV39H2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SUV39H2 BINDING SITE, designated SEQ ID:23975, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30041] Another function of VGAM766 is therefore inhibition of SUV39H2 (Accession NM\_024670), a gene which is involved in gene repression and the modification of position-effect-variegation. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SUV39H2. The function of SUV39H2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM424. Transient Receptor Potential Cation Channel, Subfamily M, Member 8 (TRPM8, Accession NM\_024080) is



another VGAM766 host target gene. TRPM8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPM8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPM8 BINDING SITE, designated SEQ ID:23517, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30042] Another function of VGAM766 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily M, Member 8 (TRPM8, Accession NM\_024080), a gene which is thought to form a receptor-activated calcium permeant cation channel. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPM8. The function of TRPM8 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM201.XT3 (Accession NM\_020208) is another VGAM766 host target gene. XT3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XT3, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XT3 BINDING SITE, designated SEQ ID:21445, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30043] Another function of VGAM766 is therefore inhibition of XT3 (Accession NM\_020208), a gene which is a Kidney-specific orphan transporter. Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XT3. The function of XT3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM21.Ac-like Transposable Element (ALTE, Accession NM\_004729) is another VGAM766 host target gene. ALTE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALTE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALTE BINDING SITE, designated SEQ ID:11104, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30044] Another function of VGAM766 is therefore inhibition of Ac-like Transposable Element (ALTE, Accession NM\_004729). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALTE. ARNTL2 (Accession NM\_020183) is another VGAM766 host target gene. ARNTL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARNTL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARNTL2 BINDING SITE, designated SEQ ID:21414, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30045] Another function of VGAM766 is therefore inhibition of ARNTL2 (Accession NM\_020183). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARNTL2. Baculoviral IAP Repeat-containing 1 (BIRC1, Accession NM\_004536) is another VGAM766 host target gene. BIRC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BIRC1, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BIRC1 BINDING SITE, designated SEQ ID:10886, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30046] Another function of VGAM766 is therefore inhibition of Baculoviral IAP Repeat-containing 1 (BIRC1, Accession NM\_004536). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BIRC1. BLOV1 (Accession XM\_083866) is another VGAM766 host target gene. BLOV1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BLOV1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLOV1 BINDING SITE, designated SEQ ID:37521, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30047] Another function of VGAM766 is therefore inhibition of BLOV1 (Accession XM\_083866). Accordingly, utilities of

VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLOV1. Chromosome 20 Open Reading Frame 108 (C20orf108, Accession NM\_080821) is another VGAM766 host target gene. C20orf108 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf108, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf108 BINDING SITE, designated SEQ ID:28085, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30048] Another function of VGAM766 is therefore inhibition of Chromosome 20 Open Reading Frame 108 (C20orf108, Accession NM\_080821). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf108. Chromosome 9 Open Reading Frame 5 (C9orf5, Accession NM\_032012) is another VGAM766 host target gene. C9orf5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C9orf5, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C9orf5 BINDING SITE, designated SEQ ID:25714, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30049] Another function of VGAM766 is therefore inhibition of Chromosome 9 Open Reading Frame 5 (C9orf5, Accession NM\_032012). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C9orf5. Ceramide Kinase (cerk, Accession NM\_022766) is another VGAM766 host target gene. cerk BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by cerk, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of cerk BINDING SITE, designated SEQ ID:23013, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30050] Another function of VGAM766 is therefore inhibition of Ceramide Kinase (cerk, Accession NM\_022766). Accord-

ingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with cerk. CG012 (Accession XM\_096710) is another VGAM766 host target gene. CG012 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CG012, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CG012 BINDING SITE, designated SEQ ID:40488, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30051] Another function of VGAM766 is therefore inhibition of CG012 (Accession XM\_096710). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CG012. COE2 (Accession XM\_034639) is another VGAM766 host target gene. COE2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by COE2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COE2 BINDING SITE, designated SEQ

ID:32127, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30052] Another function of VGAM766 is therefore inhibition of COE2 (Accession XM\_034639). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COE2. DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 34 (DDX34, Accession NM\_014681) is another VGAM766 host target gene. DDX34 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DDX34, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDX34 BINDING SITE, designated SEQ ID:16162, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30053] Another function of VGAM766 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 34 (DDX34, Accession NM\_014681). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DDX34.



DIS3 (Accession NM\_014953) is another VGAM766 host target gene. DIS3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DIS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DIS3 BINDING SITE, designated SEQ ID:17301, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30054] Another function of VGAM766 is therefore inhibition of DIS3 (Accession NM\_014953). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIS3. DKFZP434I1735 (Accession XM\_113763) is another VGAM766 host target gene. DKFZP434I1735 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP434I1735, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434I1735 BINDING SITE, designated SEQ ID:42421, to the nucleotide sequence of VGAM766 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3477.

[30055] Another function of VGAM766 is therefore inhibition of DKFZP434I1735 (Accession XM\_113763). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434I1735. DKFZP564B1023 (Accession NM\_031306) is another VGAM766 host target gene. DKFZP564B1023 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564B1023, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564B1023 BINDING SITE, designated SEQ ID:25343, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30056] Another function of VGAM766 is therefore inhibition of DKFZP564B1023 (Accession NM\_031306). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564B1023. DKFZP586D2223 (Accession NM\_018561) is another VGAM766 host target gene. DKFZP586D2223 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by DKFZP586D2223, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586D2223 BINDING SITE, designated SEQ ID:20645, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30057] Another function of VGAM766 is therefore inhibition of DKFZP586D2223 (Accession NM\_018561). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586D2223. DKFZp586I021 (Accession NM\_032271) is another VGAM766 host target gene. DKFZp586I021 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp586I021, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp586I021 BINDING SITE, designated SEQ ID:26018, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30058] Another function of VGAM766 is therefore inhibition of DKFZp586I021 (Accession NM\_032271). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp586I021. DKFZp761J139 (Accession NM\_032280) is another VGAM766 host target gene. DKFZp761J139 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp761J139, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761J139 BINDING SITE, designated SEQ ID:26036, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30059] Another function of VGAM766 is therefore inhibition of DKFZp761J139 (Accession NM\_032280). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761J139. ERAP140 (Accession XM\_059748) is another VGAM766 host target gene. ERAP140 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ERAP140, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ERAP140 BINDING SITE, designated SEQ ID:37086, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30060] Another function of VGAM766 is therefore inhibition of ERAP140 (Accession XM\_059748). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ERAP140. F-box Only Protein 27 (FBXO27, Accession XM\_059045) is another VGAM766 host target gene. FBXO27 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FBXO27, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO27 BINDING SITE, designated SEQ ID:36836, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30061] Another function of VGAM766 is therefore inhibition of F-box Only Protein 27 (FBXO27, Accession XM\_059045). Accordingly, utilities of VGAM766 include diagnosis, preven-

tion and treatment of diseases and clinical conditions associated with FBXO27. FK506 Binding Protein 14, 22 KDa (FKBP14, Accession NM\_017946) is another VGAM766 host target gene. FKBP14 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FKBP14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FKBP14 BINDING SITE, designated SEQ ID:19645, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30062] Another function of VGAM766 is therefore inhibition of FK506 Binding Protein 14, 22 KDa (FKBP14, Accession NM\_017946). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FKBP14. FLJ10008 (Accession NM\_017970) is another VGAM766 host target gene. FLJ10008 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10008, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of FLJ10008 BINDING SITE, designated SEQ ID:19692, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30063] Another function of VGAM766 is therefore inhibition of FLJ10008 (Accession NM\_017970). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10008. FLJ10650 (Accession NM\_018168) is another VGAM766 host target gene. FLJ10650 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10650, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10650 BINDING SITE, designated SEQ ID:19986, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30064] Another function of VGAM766 is therefore inhibition of FLJ10650 (Accession NM\_018168). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10650. FLJ10803 (Accession NM\_018224) is another VGAM766

host target gene. FLJ10803 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10803, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10803 BINDING SITE, designated SEQ ID:20155, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30065] Another function of VGAM766 is therefore inhibition of FLJ10803 (Accession NM\_018224). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10803. FLJ11151 (Accession XM\_042224) is another VGAM766 host target gene. FLJ11151 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11151, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11151 BINDING SITE, designated SEQ ID:33706, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.



[30066] Another function of VGAM766 is therefore inhibition of FLJ11151 (Accession XM\_042224). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11151. FLJ11700 (Accession NM\_024892) is another VGAM766 host target gene. FLJ11700 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11700 BINDING SITE, designated SEQ ID:24367, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30067] Another function of VGAM766 is therefore inhibition of FLJ11700 (Accession NM\_024892). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11700. FLJ12800 (Accession NM\_022903) is another VGAM766 host target gene. FLJ12800 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12800, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

**BINDING SITE III.** Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12800 BINDING SITE, designated SEQ ID:23191, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30068] Another function of VGAM766 is therefore inhibition of FLJ12800 (Accession NM\_022903). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12800. FLJ14641 (Accession NM\_032817) is another VGAM766 host target gene. FLJ14641 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14641, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14641 BINDING SITE, designated SEQ ID:26587, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30069] Another function of VGAM766 is therefore inhibition of FLJ14641 (Accession NM\_032817). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14641.

FLJ20013 (Accession NM\_017621) is another VGAM766 host target gene. FLJ20013 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20013, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20013 BINDING SITE, designated SEQ ID:19121, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30070] Another function of VGAM766 is therefore inhibition of FLJ20013 (Accession NM\_017621). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20013. FLJ20211 (Accession NM\_017713) is another VGAM766 host target gene. FLJ20211 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20211, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20211 BINDING SITE, designated SEQ ID:19296, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3477.

[30071] Another function of VGAM766 is therefore inhibition of FLJ20211 (Accession NM\_017713). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20211. FLJ20783 (Accession NM\_017958) is another VGAM766 host target gene. FLJ20783 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20783, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20783 BINDING SITE, designated SEQ ID:19670, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30072] Another function of VGAM766 is therefore inhibition of FLJ20783 (Accession NM\_017958). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20783. FLJ20825 (Accession NM\_017962) is another VGAM766 host target gene. FLJ20825 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20825, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20825 BINDING SITE, designated SEQ ID:19681, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30073] Another function of VGAM766 is therefore inhibition of FLJ20825 (Accession NM\_017962). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20825. FLJ21687 (Accession NM\_024859) is another VGAM766 host target gene. FLJ21687 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21687, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21687 BINDING SITE, designated SEQ ID:24289, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30074] Another function of VGAM766 is therefore inhibition of FLJ21687 (Accession NM\_024859). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ21687. FLJ21870 (Accession NM\_023016) is another VGAM766 host target gene. FLJ21870 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21870, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21870 BINDING SITE, designated SEQ ID:23280, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30075] Another function of VGAM766 is therefore inhibition of FLJ21870 (Accession NM\_023016). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21870. FLJ22692 (Accession NM\_025049) is another VGAM766 host target gene. FLJ22692 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22692, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22692 BINDING SITE, designated SEQ ID:24645, to the nucleotide sequence of

VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30076] Another function of VGAM766 is therefore inhibition of FLJ22692 (Accession NM\_025049). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22692. FLJ22814 (Accession NM\_024916) is another VGAM766 host target gene. FLJ22814 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22814, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22814 BINDING SITE, designated SEQ ID:24441, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30077] Another function of VGAM766 is therefore inhibition of FLJ22814 (Accession NM\_024916). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22814. FLJ23235 (Accession NM\_024943) is another VGAM766 host target gene. FLJ23235 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ23235, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23235 BINDING SITE, designated SEQ ID:24488, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30078] Another function of VGAM766 is therefore inhibition of FLJ23235 (Accession NM\_024943). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23235. FLJ31737 (Accession NM\_144984) is another VGAM766 host target gene. FLJ31737 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ31737, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ31737 BINDING SITE, designated SEQ ID:29590, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30079] Another function of VGAM766 is therefore inhibition of FLJ31737 (Accession NM\_144984). Accordingly, utilities of



VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ31737. KIAA0252 (Accession XM\_031646) is another VGAM766 host target gene. KIAA0252 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0252, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0252 BINDING SITE, designated SEQ ID:31448, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30080] Another function of VGAM766 is therefore inhibition of KIAA0252 (Accession XM\_031646). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0252. KIAA0266 (Accession NM\_021645) is another VGAM766 host target gene. KIAA0266 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0266, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA0266 BINDING SITE, designated SEQ ID:22310, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30081] Another function of VGAM766 is therefore inhibition of KIAA0266 (Accession NM\_021645). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0266. KIAA0420 (Accession XM\_032693) is another VGAM766 host target gene. KIAA0420 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0420 BINDING SITE, designated SEQ ID:31723, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30082] Another function of VGAM766 is therefore inhibition of KIAA0420 (Accession XM\_032693). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0420. KIAA0472 (Accession XM\_050147) is another VGAM766 host target gene. KIAA0472 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0472, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0472 BINDING SITE, designated SEQ ID:35578, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30083] Another function of VGAM766 is therefore inhibition of KIAA0472 (Accession XM\_050147). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0472. KIAA0527 (Accession XM\_171054) is another VGAM766 host target gene. KIAA0527 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0527, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0527 BINDING SITE, designated SEQ ID:45841, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30084] Another function of VGAM766 is therefore inhibition of

KIAA0527 (Accession XM\_171054). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0527. KIAA0794 (Accession XM\_087353) is another VGAM766 host target gene. KIAA0794 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0794, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0794 BINDING SITE, designated SEQ ID:39181, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30085] Another function of VGAM766 is therefore inhibition of KIAA0794 (Accession XM\_087353). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0794. KIAA1228 (Accession XM\_036408) is another VGAM766 host target gene. KIAA1228 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1228 BINDING SITE, designated SEQ ID:32444, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30086] Another function of VGAM766 is therefore inhibition of KIAA1228 (Accession XM\_036408). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1228. KIAA1641 (Accession XM\_087167) is another VGAM766 host target gene. KIAA1641 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1641, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1641 BINDING SITE, designated SEQ ID:39100, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30087] Another function of VGAM766 is therefore inhibition of KIAA1641 (Accession XM\_087167). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1641. KIAA1871 (Accession XM\_028409) is another

VGAM766 host target gene. KIAA1871 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1871, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1871 BINDING SITE, designated SEQ ID:30705, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30088] Another function of VGAM766 is therefore inhibition of KIAA1871 (Accession XM\_028409). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1871. KIAA1872 (Accession XM\_031917) is another VGAM766 host target gene. KIAA1872 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1872, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1872 BINDING SITE, designated SEQ ID:31519, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30089] Another function of VGAM766 is therefore inhibition of KIAA1872 (Accession XM\_031917). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1872. KIAA1969 (Accession XM\_086098) is another VGAM766 host target gene. KIAA1969 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1969, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1969 BINDING SITE, designated SEQ ID:38491, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30090] Another function of VGAM766 is therefore inhibition of KIAA1969 (Accession XM\_086098). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1969. KR18 (Accession NM\_033288) is another VGAM766 host target gene. KR18 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KR18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KR18 BINDING SITE, designated SEQ ID:27118, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30091] Another function of VGAM766 is therefore inhibition of KR18 (Accession NM\_033288). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KR18. LIM (Accession NM\_006457) is another VGAM766 host target gene. LIM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LIM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LIM BINDING SITE, designated SEQ ID:13178, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30092] Another function of VGAM766 is therefore inhibition of LIM (Accession NM\_006457). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LIM. LRG (Accession NM\_052972) is another VGAM766 host target



gene. LRG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LRG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRG BINDING SITE, designated SEQ ID:27546, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30093] Another function of VGAM766 is therefore inhibition of LRG (Accession NM\_052972). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRG. Mesoderm Development Candidate 2 (MESDC2, Accession XM\_051854) is another VGAM766 host target gene. MESDC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MESDC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MESDC2 BINDING SITE, designated SEQ ID:35893, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30094] Another function of VGAM766 is therefore inhibition of Mesoderm Development Candidate 2 (MESDC2, Accession XM\_051854). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MESDC2. MGC14407 (Accession NM\_032908) is another VGAM766 host target gene. MGC14407 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC14407, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC14407 BINDING SITE, designated SEQ ID:26728, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30095] Another function of VGAM766 is therefore inhibition of MGC14407 (Accession NM\_032908). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC14407. MGC2562 (Accession NM\_032374) is another VGAM766 host target gene. MGC2562 BINDING SITE1 and MGC2562 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by

MGC2562, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2562 BINDING SITE1 and MGC2562 BINDING SITE2, designated SEQ ID:26162 and SEQ ID:26164 respectively, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30096] Another function of VGAM766 is therefore inhibition of MGC2562 (Accession NM\_032374). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2562. MGC4840 (Accession XM\_049476) is another VGAM766 host target gene. MGC4840 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4840, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4840 BINDING SITE, designated SEQ ID:35439, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30097] Another function of VGAM766 is therefore inhibition of

MGC4840 (Accession XM\_049476). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4840. PRO0478 (Accession NM\_014129) is another VGAM766 host target gene. PRO0478 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO0478, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0478 BINDING SITE, designated SEQ ID:15397, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30098] Another function of VGAM766 is therefore inhibition of PRO0478 (Accession NM\_014129). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0478. Rpo1-2 (Accession NM\_019014) is another VGAM766 host target gene. Rpo1-2 BINDING SITE1 and Rpo1-2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by Rpo1-2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of Rpo1-2 BINDING SITE1 and Rpo1-2 BINDING SITE2, designated SEQ ID:21102 and SEQ ID:21103 respectively, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30099] Another function of VGAM766 is therefore inhibition of Rpo1-2 (Accession NM\_019014). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rpo1-2. Sodium Channel, Voltage-gated, Type XII, Alpha Polypeptide (SCN12A, Accession NM\_014139) is another VGAM766 host target gene. SCN12A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCN12A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCN12A BINDING SITE, designated SEQ ID:15409, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30100] Another function of VGAM766 is therefore inhibition of Sodium Channel, Voltage-gated, Type XII, Alpha Polypeptide (SCN12A, Accession NM\_014139). Accordingly, utili-

ties of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCN12A. Serine Palmitoyltransferase, Long Chain Base Subunit 2 (SPTLC2, Accession NM\_004863) is another VGAM766 host target gene. SPTLC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SPTLC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPTLC2 BINDING SITE, designated SEQ ID:11281, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30101] Another function of VGAM766 is therefore inhibition of Serine Palmitoyltransferase, Long Chain Base Subunit 2 (SPTLC2, Accession NM\_004863). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPTLC2. TRIAD3 (Accession XM\_170517) is another VGAM766 host target gene. TRIAD3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIAD3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BIND-

ING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIAD3 BINDING SITE, designated SEQ ID:45347, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30102] Another function of VGAM766 is therefore inhibition of TRIAD3 (Accession XM\_170517). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIAD3. Williams–Beuren Syndrome Chromosome Region 23 (WBSCR23, Accession NM\_025042) is another VGAM766 host target gene. WBSCR23 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by WBSCR23, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WBSCR23 BINDING SITE, designated SEQ ID:24640, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30103] Another function of VGAM766 is therefore inhibition of Williams–Beuren Syndrome Chromosome Region 23 (WBSCR23, Accession NM\_025042). Accordingly, utilities

of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WB-SCR23. WSB1 (Accession NM\_134264) is another VGAM766 host target gene. WSB1 BINDING SITE1 and WSB1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by WSB1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WSB1 BINDING SITE1 and WSB1 BINDING SITE2, designated SEQ ID:28615 and SEQ ID:28621 respectively, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30104] Another function of VGAM766 is therefore inhibition of WSB1 (Accession NM\_134264). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WSB1. LOC115129 (Accession XM\_055292) is another VGAM766 host target gene. LOC115129 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC115129, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-



tarity of the nucleotide sequences of LOC115129 BINDING SITE, designated SEQ ID:36251, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30105] Another function of VGAM766 is therefore inhibition of LOC115129 (Accession XM\_055292). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115129. LOC127428 (Accession XM\_059144) is another VGAM766 host target gene. LOC127428 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC127428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127428 BINDING SITE, designated SEQ ID:36896, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30106] Another function of VGAM766 is therefore inhibition of LOC127428 (Accession XM\_059144). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127428. LOC134147 (Accession NM\_138809) is an-

other VGAM766 host target gene. LOC134147 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC134147, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC134147 BINDING SITE, designated SEQ ID:29031, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30107] Another function of VGAM766 is therefore inhibition of LOC134147 (Accession NM\_138809). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC134147. LOC145988 (Accession XM\_085290) is another VGAM766 host target gene. LOC145988 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145988, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145988 BINDING SITE, designated SEQ ID:38038, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30108] Another function of VGAM766 is therefore inhibition of LOC145988 (Accession XM\_085290). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145988. LOC146229 (Accession XM\_085387) is another VGAM766 host target gene. LOC146229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146229 BINDING SITE, designated SEQ ID:38110, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30109] Another function of VGAM766 is therefore inhibition of LOC146229 (Accession XM\_085387). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146229. LOC147837 (Accession XM\_085915) is another VGAM766 host target gene. LOC147837 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147837, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147837 BINDING SITE, designated SEQ ID:38393, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30110] Another function of VGAM766 is therefore inhibition of LOC147837 (Accession XM\_085915). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147837. LOC148147 (Accession XM\_086071) is another VGAM766 host target gene. LOC148147 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148147, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148147 BINDING SITE, designated SEQ ID:38476, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30111] Another function of VGAM766 is therefore inhibition of LOC148147 (Accession XM\_086071). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC148147. LOC148254 (Accession XM\_086121) is another VGAM766 host target gene. LOC148254 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148254, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148254 BINDING SITE, designated SEQ ID:38502, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30112] Another function of VGAM766 is therefore inhibition of LOC148254 (Accession XM\_086121). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148254. LOC149705 (Accession XM\_097711) is another VGAM766 host target gene. LOC149705 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149705, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149705 BINDING SITE, designated SEQ ID:41052, to the nucleotide sequence of VGAM766 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3477.

[30113] Another function of VGAM766 is therefore inhibition of LOC149705 (Accession XM\_097711). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149705. LOC150245 (Accession XM\_097843) is another VGAM766 host target gene. LOC150245 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150245, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150245 BINDING SITE, designated SEQ ID:41162, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30114] Another function of VGAM766 is therefore inhibition of LOC150245 (Accession XM\_097843). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150245. LOC150481 (Accession XM\_086929) is another VGAM766 host target gene. LOC150481 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150481, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150481 BINDING SITE, designated SEQ ID:38980, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30115] Another function of VGAM766 is therefore inhibition of LOC150481 (Accession XM\_086929). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150481. LOC151248 (Accession XM\_087143) is another VGAM766 host target gene. LOC151248 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151248, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151248 BINDING SITE, designated SEQ ID:39088, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30116] Another function of VGAM766 is therefore inhibition of LOC151248 (Accession XM\_087143). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC151248. LOC152426 (Accession XM\_098225) is another VGAM766 host target gene. LOC152426 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152426, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152426 BINDING SITE, designated SEQ ID:41499, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30117] Another function of VGAM766 is therefore inhibition of LOC152426 (Accession XM\_098225). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152426. LOC153727 (Accession XM\_098422) is another VGAM766 host target gene. LOC153727 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153727, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153727 BINDING SITE, designated SEQ ID:41681, to



the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30118] Another function of VGAM766 is therefore inhibition of LOC153727 (Accession XM\_098422). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153727. LOC155006 (Accession XM\_088117) is another VGAM766 host target gene. LOC155006 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC155006, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155006 BINDING SITE, designated SEQ ID:39526, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30119] Another function of VGAM766 is therefore inhibition of LOC155006 (Accession XM\_088117). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155006. LOC158088 (Accession XM\_098872) is another VGAM766 host target gene. LOC158088 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC158088, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158088 BINDING SITE, designated SEQ ID:41917, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30120] Another function of VGAM766 is therefore inhibition of LOC158088 (Accession XM\_098872). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158088. LOC158677 (Accession XM\_098976) is another VGAM766 host target gene. LOC158677 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158677, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158677 BINDING SITE, designated SEQ ID:42023, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30121] Another function of VGAM766 is therefore inhibition of LOC158677 (Accession XM\_098976). Accordingly, utilities

of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158677. LOC158819 (Accession XM\_098995) is another VGAM766 host target gene. LOC158819 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158819, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158819 BINDING SITE, designated SEQ ID:42026, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30122] Another function of VGAM766 is therefore inhibition of LOC158819 (Accession XM\_098995). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158819. LOC159036 (Accession XM\_099018) is another VGAM766 host target gene. LOC159036 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC159036, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC159036 BINDING SITE, designated SEQ ID:42054, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30123] Another function of VGAM766 is therefore inhibition of LOC159036 (Accession XM\_099018). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC159036. LOC200251 (Accession XM\_114173) is another VGAM766 host target gene. LOC200251 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200251 BINDING SITE, designated SEQ ID:42756, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30124] Another function of VGAM766 is therefore inhibition of LOC200251 (Accession XM\_114173). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200251. LOC201220 (Accession XM\_113321) is another VGAM766 host target gene. LOC201220 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC201220, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201220 BINDING SITE, designated SEQ ID:42224, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30125] Another function of VGAM766 is therefore inhibition of LOC201220 (Accession XM\_113321). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201220. LOC201895 (Accession XM\_114396) is another VGAM766 host target gene. LOC201895 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC201895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201895 BINDING SITE, designated SEQ ID:42926, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30126] Another function of VGAM766 is therefore inhibition of

LOC201895 (Accession XM\_114396). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201895. LOC203378 (Accession XM\_117541) is another VGAM766 host target gene. LOC203378 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203378, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203378 BINDING SITE, designated SEQ ID:43553, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30127] Another function of VGAM766 is therefore inhibition of LOC203378 (Accession XM\_117541). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203378. LOC220662 (Accession XM\_165978) is another VGAM766 host target gene. LOC220662 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220662, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC220662 BINDING SITE, designated SEQ ID:43823, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30128] Another function of VGAM766 is therefore inhibition of LOC220662 (Accession XM\_165978). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220662. LOC221477 (Accession XM\_166397) is another VGAM766 host target gene. LOC221477 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221477, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221477 BINDING SITE, designated SEQ ID:44254, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30129] Another function of VGAM766 is therefore inhibition of LOC221477 (Accession XM\_166397). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221477. LOC221543 (Accession XM\_168091) is an-

other VGAM766 host target gene. LOC221543 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC221543, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221543 BINDING SITE, designated SEQ ID:45013, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30130] Another function of VGAM766 is therefore inhibition of LOC221543 (Accession XM\_168091). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221543. LOC221755 (Accession XM\_166465) is another VGAM766 host target gene. LOC221755 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221755, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221755 BINDING SITE, designated SEQ ID:44386, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.



[30131] Another function of VGAM766 is therefore inhibition of LOC221755 (Accession XM\_166465). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221755. LOC254122 (Accession XM\_170660) is another VGAM766 host target gene. LOC254122 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254122, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254122 BINDING SITE, designated SEQ ID:45436, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30132] Another function of VGAM766 is therefore inhibition of LOC254122 (Accession XM\_170660). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254122. LOC255196 (Accession XM\_173157) is another VGAM766 host target gene. LOC255196 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255196, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255196 BINDING SITE, designated SEQ ID:46413, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30133] Another function of VGAM766 is therefore inhibition of LOC255196 (Accession XM\_173157). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255196. LOC257354 (Accession XM\_170810) is another VGAM766 host target gene. LOC257354 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257354, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257354 BINDING SITE, designated SEQ ID:45576, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30134] Another function of VGAM766 is therefore inhibition of LOC257354 (Accession XM\_170810). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC257354. LOC51336 (Accession NM\_016646) is another VGAM766 host target gene. LOC51336 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51336, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51336 BINDING SITE, designated SEQ ID:18757, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30135] Another function of VGAM766 is therefore inhibition of LOC51336 (Accession NM\_016646). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51336. LOC90979 (Accession XM\_035323) is another VGAM766 host target gene. LOC90979 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90979, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90979 BINDING SITE, designated SEQ ID:32232, to the nucleotide sequence of VGAM766 RNA, herein designated

VGAM RNA, also designated SEQ ID:3477.

[30136] Another function of VGAM766 is therefore inhibition of LOC90979 (Accession XM\_035323). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90979. LOC92078 (Accession XM\_042684) is another VGAM766 host target gene. LOC92078 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92078 BINDING SITE, designated SEQ ID:33743, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30137] Another function of VGAM766 is therefore inhibition of LOC92078 (Accession XM\_042684). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92078. LOC92421 (Accession XM\_044996) is another VGAM766 host target gene. LOC92421 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92421, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92421 BINDING SITE, designated SEQ ID:34310, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30138] Another function of VGAM766 is therefore inhibition of LOC92421 (Accession XM\_044996). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92421. LOC92771 (Accession NM\_033424) is another VGAM766 host target gene. LOC92771 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92771, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92771 BINDING SITE, designated SEQ ID:27249, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30139] Another function of VGAM766 is therefore inhibition of LOC92771 (Accession NM\_033424). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC92771. LOC93132 (Accession XM\_049396) is another VGAM766 host target gene. LOC93132 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC93132, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93132 BINDING SITE, designated SEQ ID:35409, to the nucleotide sequence of VGAM766 RNA, herein designated VGAM RNA, also designated SEQ ID:3477.

[30140] Another function of VGAM766 is therefore inhibition of LOC93132 (Accession XM\_049396). Accordingly, utilities of VGAM766 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93132. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 767 (VGAM767) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30141] VGAM767 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM767 was detected is described hereinabove with reference to Figs. 1–8.

[30142] VGAM767 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM767 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30143] VGAM767 gene encodes a VGAM767 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM767 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM767 precursor RNA is designated SEQ ID:753, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:753 is located at position 6557 relative to the genome of Bovine Coronavirus.

[30144] VGAM767 precursor RNA folds onto itself, forming VGAM767 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30145] An enzyme complex designated DICER COMPLEX, `dices` the VGAM767 folded precursor RNA into VGAM767 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 68%) nucleotide sequence of VGAM767 RNA is designated SEQ ID:3478, and is provided hereinbelow with reference to the sequence listing part.

[30146] VGAM767 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM767 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM767 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.



[30147] VGAM767 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM767 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM767 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM767 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM767 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30148] The complementary binding of VGAM767 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM767 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM767 host target RNA into VGAM767 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30149] It is appreciated that VGAM767 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM767 host target genes. The mRNA of each one of this plurality of VGAM767 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM767 RNA, herein designated VGAM RNA, and which when bound by VGAM767 RNA causes inhibition of translation of respective one or more VGAM767 host target proteins.

[30150] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM767 gene, herein designated VGAM GENE, on one or more VGAM767 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30151] It is yet further appreciated that a function of VGAM767 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM767 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM767 correlate with, and may be deduced from, the identity of the host target genes which VGAM767 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30152] Nucleotide sequences of the VGAM767 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM767 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM767 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM767 are further described hereinbelow with reference to Table 1.

[30153] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM767 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM767 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30154] As mentioned hereinabove with reference to Fig. 1, a function of VGAM767 gene, herein designated VGAM is inhibition of expression of VGAM767 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM767 correlate with, and may be deduced from, the identity of the target genes which VGAM767 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30155] LOC93587 (Accession XM\_052377) is a VGAM767 host target gene. LOC93587 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA

encoded by LOC93587, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93587 BINDING SITE, designated SEQ ID:35963, to the nucleotide sequence of VGAM767 RNA, herein designated VGAM RNA, also designated SEQ ID:3478.

[30156] A function of VGAM767 is therefore inhibition of LOC93587 (Accession XM\_052377). Accordingly, utilities of VGAM767 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93587. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 768 (VGAM768) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30157] VGAM768 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM768 was detected is described hereinabove with reference to Figs. 1–8.

[30158] VGAM768 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Bovine Coronavirus. VGAM768 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30159] VGAM768 gene encodes a VGAM768 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM768 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM768 precursor RNA is designated SEQ ID:754, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:754 is located at position 13125 relative to the genome of Bovine Coronavirus.

[30160] VGAM768 precursor RNA folds onto itself, forming VGAM768 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30161] An enzyme complex designated DICER COMPLEX, `dices` the VGAM768 folded precursor RNA into VGAM768 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM768 RNA is designated SEQ ID:3479, and is provided hereinbelow with reference to the sequence listing part.

[30162] VGAM768 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM768 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM768 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30163] VGAM768 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM768 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM768 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM768 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM768 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30164] The complementary binding of VGAM768 RNA, herein designated VGAM RNA, to host target binding sites on VGAM768 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM768 host tar-



get RNA into VGAM768 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30165] It is appreciated that VGAM768 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM768 host target genes. The mRNA of each one of this plurality of VGAM768 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM768 RNA, herein designated VGAM RNA, and which when bound by VGAM768 RNA causes inhibition of translation of respective one or more VGAM768 host target proteins.

[30166] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM768 gene, herein designated VGAM GENE, on one or more VGAM768 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30167] It is yet further appreciated that a function of VGAM768 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM768 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM768 correlate with, and may be deduced from, the identity of the host target genes which VGAM768 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30168] Nucleotide sequences of the VGAM768 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM768 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM768 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM768 are further

described hereinbelow with reference to Table 1.

[30169] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM768 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM768 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30170] As mentioned hereinabove with reference to Fig. 1, a function of VGAM768 gene, herein designated VGAM is inhibition of expression of VGAM768 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM768 correlate with, and may be deduced from, the identity of the target genes which VGAM768 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30171] Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_080923) is a VGAM768 host target gene. PTPRC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTPRC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of PTPRC BINDING SITE, designated SEQ ID:28148, to the nucleotide sequence of VGAM768 RNA, herein designated VGAM RNA, also designated SEQ ID:3479.

[30172] A function of VGAM768 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, C (PTPRC, Accession NM\_080923). Accordingly, utilities of VGAM768 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRC. GLP (Accession NM\_018652) is another VGAM768 host target gene. GLP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLP BINDING SITE, designated SEQ ID:20722, to the nucleotide sequence of VGAM768 RNA, herein designated VGAM RNA, also designated SEQ ID:3479.

[30173] Another function of VGAM768 is therefore inhibition of GLP (Accession NM\_018652). Accordingly, utilities of VGAM768 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLP. LOC220538 (Accession XM\_165407) is another VGAM768

host target gene. LOC220538 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220538 BINDING SITE, designated SEQ ID:43625, to the nucleotide sequence of VGAM768 RNA, herein designated VGAM RNA, also designated SEQ ID:3479.

[30174] Another function of VGAM768 is therefore inhibition of LOC220538 (Accession XM\_165407). Accordingly, utilities of VGAM768 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220538. LOC257286 (Accession XM\_170549) is another VGAM768 host target gene. LOC257286 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257286, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257286 BINDING SITE, designated SEQ ID:45372, to the nucleotide sequence of VGAM768 RNA, herein designated VGAM RNA, also designated SEQ ID:3479.

[30175] Another function of VGAM768 is therefore inhibition of LOC257286 (Accession XM\_170549). Accordingly, utilities of VGAM768 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257286. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 769 (VGAM769) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30176] VGAM769 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM769 was detected is described hereinabove with reference to Figs. 1–8.

[30177] VGAM769 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM769 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30178] VGAM769 gene encodes a VGAM769 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM769

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM769 precursor RNA is designated SEQ ID:755, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:755 is located at position 16313 relative to the genome of Bovine Coronavirus.

[30179] VGAM769 precursor RNA folds onto itself, forming VGAM769 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30180] An enzyme complex designated DICER COMPLEX, `dices` the VGAM769 folded precursor RNA into VGAM769 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 45%) nucleotide sequence of VGAM769 RNA is designated SEQ ID:3480, and is provided hereinbelow with reference to the sequence listing part.

[30181] VGAM769 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM769 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM769 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[30182] VGAM769 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM769 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM769 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the



number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM769 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM769 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30183] The complementary binding of VGAM769 RNA, herein designated VGAM RNA, to host target binding sites on VGAM769 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM769 host target RNA into VGAM769 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30184] It is appreciated that VGAM769 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM769 host target genes. The mRNA of each one of this plurality of VGAM769 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM769 RNA, herein designated VGAM RNA, and which when bound by VGAM769 RNA causes inhibition of translation of respective one or more VGAM769 host target proteins.

[30185] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM769 gene, herein designated VGAM GENE, on one or more VGAM769 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30186] It is yet further appreciated that a function of VGAM769 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM769 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM769 correlate with, and may be deduced from, the identity of the host target genes which VGAM769 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30187] Nucleotide sequences of the VGAM769 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM769 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM769 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM769 are further described hereinbelow with reference to Table 1.

[30188] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM769 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM769 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[30189] As mentioned hereinabove with reference to Fig. 1, a function of VGAM769 gene, herein designated VGAM is inhibition of expression of VGAM769 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM769 correlate with, and may be deduced from, the identity of the target genes which VGAM769 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30190] Ankyrin 2, Neuronal (ANK2, Accession NM\_001148) is a VGAM769 host target gene. ANK2 BINDING SITE1 and ANK2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ANK2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANK2 BINDING SITE1 and ANK2 BINDING SITE2, designated SEQ ID:6820 and SEQ ID:21964 respectively, to the nucleotide sequence of VGAM769 RNA, herein designated VGAM RNA, also designated SEQ ID:3480.

[30191] A function of VGAM769 is therefore inhibition of Ankyrin 2, Neuronal (ANK2, Accession NM\_001148), a gene which attaches integral membrane proteins to cytoskeletal ele-

ments. also binds to cytoskeletal proteins. Accordingly, utilities of VGAM769 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANK2. The function of ANK2 has been established by previous studies. Tse et al. (1991) studied immunoreactive isoforms of erythrocyte ankyrin found in nonerythroid tissues. Using an erythrocyte ankyrin cDNA clone as a hybridization probe, they isolated a clone from a human genomic library that hybridized at low but not at high stringency. Further studies suggested that the clone represented part of a gene for nonerythroid ankyrin, which they designated ANK2. By analysis of somatic cell hybrids and by fluorescence in situ hybridization, they assigned ANK2 to 4q25–q27. Otto et al. (1991) isolated and sequenced cDNAs related to 2 brain ankyrin isoforms and showed that they are produced through alternative splicing of the mRNA from a single gene. By analysis of human/rodent cell hybrids, Otto et al. (1991) assigned the brain ankyrin gene to chromosome 4.

[30192] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30193] Otto, E.; Kunitomo, M.; McLaughlin, T.; Bennett, V. : Isola-

tion and characterization of cDNAs encoding human brain ankyrins reveal a family of alternatively spliced genes. J. Cell Biol. 114: 241–253, 1991. ; and

[30194] Tse, W. T.; Menninger, J. C.; Yang–Feng, T. L.; Francke, U.; Sahr, K. E.; Lux, S. E.; Ward, D. C.; Forget, B. G. : Isolation and chromosomal localization of a novel non–erythroid ankyri.

[30195] Further studies establishing the function and utilities of ANK2 are found in John Hopkins OMIM database record ID 106410, and in cited publications numbered 4840–4841 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transmembrane 4 Superfamily Member 6 (TM4SF6, Accession NM\_003270) is another VGAM769 host target gene. TM4SF6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TM4SF6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TM4SF6 BINDING SITE, designated SEQ ID:9283, to the nucleotide sequence of VGAM769 RNA, herein designated VGAM RNA, also designated SEQ ID:3480.

[30196] Another function of VGAM769 is therefore inhibition of

Transmembrane 4 Superfamily Member 6 (TM4SF6, Accession NM\_003270), a gene which plays a role in the regulation of cell development, activation, growth and motility. Accordingly, utilities of VGAM769 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TM4SF6. The function of TM4SF6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM84.FLJ12595 (Accession NM\_024994) is another VGAM769 host target gene. FLJ12595 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12595, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12595 BINDING SITE, designated SEQ ID:24556, to the nucleotide sequence of VGAM769 RNA, herein designated VGAM RNA, also designated SEQ ID:3480.

[30197] Another function of VGAM769 is therefore inhibition of FLJ12595 (Accession NM\_024994). Accordingly, utilities of VGAM769 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12595.

KIAA1582 (Accession XM\_037262) is another VGAM769 host target gene. KIAA1582 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1582, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1582 BINDING SITE, designated SEQ ID:32591, to the nucleotide sequence of VGAM769 RNA, herein designated VGAM RNA, also designated SEQ ID:3480.

[30198] Another function of VGAM769 is therefore inhibition of KIAA1582 (Accession XM\_037262). Accordingly, utilities of VGAM769 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1582. LOC196993 (Accession XM\_116971) is another VGAM769 host target gene. LOC196993 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC196993, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196993 BINDING SITE, designated SEQ ID:43159, to the nucleotide sequence of VGAM769 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3480.

[30199] Another function of VGAM769 is therefore inhibition of LOC196993 (Accession XM\_116971). Accordingly, utilities of VGAM769 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196993. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 770 (VGAM770) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30200] VGAM770 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM770 was detected is described hereinabove with reference to Figs. 1–8.

[30201] VGAM770 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM770 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30202] VGAM770 gene encodes a VGAM770 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM770 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM770 precursor RNA is designated SEQ ID:756, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:756 is located at position 13249 relative to the genome of Bovine Coronavirus.

[30203] VGAM770 precursor RNA folds onto itself, forming VGAM770 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30204] An enzyme complex designated DICER COMPLEX, `dices` the VGAM770 folded precursor RNA into VGAM770 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM770 RNA is designated SEQ ID:3481, and is provided hereinbelow with reference to the sequence listing part.

[30205] VGAM770 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM770 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM770 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[30206] VGAM770 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM770 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM770 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM770 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM770 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[30207] The complementary binding of VGAM770 RNA, herein designated VGAM RNA, to host target binding sites on VGAM770 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM770 host target RNA into VGAM770 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30208] It is appreciated that VGAM770 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM770 host target genes. The mRNA of

each one of this plurality of VGAM770 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM770 RNA, herein designated VGAM RNA, and which when bound by VGAM770 RNA causes inhibition of translation of respective one or more VGAM770 host target proteins.

[30209] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM770 gene, herein designated VGAM GENE, on one or more VGAM770 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[30210] It is yet further appreciated that a function of VGAM770 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM770 correlate with, and may be deduced from, the identity of the host target genes which VGAM770 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30211] Nucleotide sequences of the VGAM770 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM770 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM770 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM770 are further described hereinbelow with reference to Table 1.

[30212] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM770 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM770 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[30213] As mentioned hereinabove with reference to Fig. 1, a function of VGAM770 gene, herein designated VGAM is inhibition of expression of VGAM770 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM770 correlate with, and may be deduced from, the identity of the target genes which VGAM770 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30214] Glutamate Receptor, Metabotropic 7 (GRM7, Accession NM\_000844) is a VGAM770 host target gene. GRM7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRM7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRM7 BINDING SITE, designated SEQ ID:6518, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30215] A function of VGAM770 is therefore inhibition of Glutamate Receptor, Metabotropic 7 (GRM7, Accession NM\_000844), a gene which is mediated by a g-protein

that inhibits adenylate cyclase activity. Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRM7. The function of GRM7 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM746. Mannosyl (alpha-1,6-)-glycoprotein Beta-1,6-N-acetyl-glucosaminyltransferase (MGAT5, Accession NM\_002410) is another VGAM770 host target gene. MGAT5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGAT5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAT5 BINDING SITE, designated SEQ ID:8240, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30216] Another function of VGAM770 is therefore inhibition of Mannosyl (alpha-1,6-)-glycoprotein Beta-1,6-N-acetyl-glucosaminyltransferase (MGAT5, Accession NM\_002410). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clini-



cal conditions associated with MGAT5. X-box Binding Protein 1 (XBP1, Accession NM\_005080) is another VGAM770 host target gene. XBP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by XBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XBP1 BINDING SITE, designated SEQ ID:11533, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30217] Another function of VGAM770 is therefore inhibition of X-box Binding Protein 1 (XBP1, Accession NM\_005080), a gene which has a role in transcriptional regulation. Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XBP1. The function of XBP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM746.DKFZP434B044 (Accession NM\_031476) is another VGAM770 host target gene. DKFZP434B044 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA en-

coded by DKFZP434B044, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434B044 BINDING SITE, designated SEQ ID:25553, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30218] Another function of VGAM770 is therefore inhibition of DKFZP434B044 (Accession NM\_031476). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434B044. FLJ12806 (Accession NM\_022831) is another VGAM770 host target gene. FLJ12806 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12806, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12806 BINDING SITE, designated SEQ ID:23112, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30219] Another function of VGAM770 is therefore inhibition of FLJ12806 (Accession NM\_022831). Accordingly, utilities of

VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12806. FLJ22635 (Accession NM\_025092) is another VGAM770 host target gene. FLJ22635 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22635, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22635 BINDING SITE, designated SEQ ID:24716, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30220] Another function of VGAM770 is therefore inhibition of FLJ22635 (Accession NM\_025092). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22635. FLJ23604 (Accession NM\_025064) is another VGAM770 host target gene. FLJ23604 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23604, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23604 BINDING SITE,

designated SEQ ID:24661, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30221] Another function of VGAM770 is therefore inhibition of FLJ23604 (Accession NM\_025064). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23604. KIAA0557 (Accession XM\_085507) is another VGAM770 host target gene. KIAA0557 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0557, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0557 BINDING SITE, designated SEQ ID:38202, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30222] Another function of VGAM770 is therefore inhibition of KIAA0557 (Accession XM\_085507). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0557. LOC144742 (Accession XM\_084949) is another VGAM770 host target gene. LOC144742 BINDING SITE is

HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144742, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144742 BINDING SITE, designated SEQ ID:37777, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30223] Another function of VGAM770 is therefore inhibition of LOC144742 (Accession XM\_084949). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144742. LOC145842 (Accession XM\_085254) is another VGAM770 host target gene. LOC145842 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145842, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145842 BINDING SITE, designated SEQ ID:37997, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30224] Another function of VGAM770 is therefore inhibition of

LOC145842 (Accession XM\_085254). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145842. LOC153711 (Accession XM\_098419) is another VGAM770 host target gene. LOC153711 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153711, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153711 BINDING SITE, designated SEQ ID:41668, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30225] Another function of VGAM770 is therefore inhibition of LOC153711 (Accession XM\_098419). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153711. LOC51008 (Accession NM\_015947) is another VGAM770 host target gene. LOC51008 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51008, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of LOC51008 BINDING SITE, designated SEQ ID:18064, to the nucleotide sequence of VGAM770 RNA, herein designated VGAM RNA, also designated SEQ ID:3481.

[30226] Another function of VGAM770 is therefore inhibition of LOC51008 (Accession NM\_015947). Accordingly, utilities of VGAM770 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51008. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 771 (VGAM771) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30227] VGAM771 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM771 was detected is described hereinabove with reference to Figs. 1–8.

[30228] VGAM771 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM771 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[30229] VGAM771 gene encodes a VGAM771 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM771 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM771 precursor RNA is designated SEQ ID:757, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:757 is located at position 25459 relative to the genome of Bovine Coronavirus.

[30230] VGAM771 precursor RNA folds onto itself, forming VGAM771 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30231] An enzyme complex designated DICER COMPLEX, `dices` the VGAM771 folded precursor RNA into VGAM771 RNA, herein designated VGAM RNA, a single stranded ~22 nt



long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 65%) nucleotide sequence of VGAM771 RNA is designated SEQ ID:3482, and is provided hereinbelow with reference to the sequence listing part.

[30232] VGAM771 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM771 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM771 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30233] VGAM771 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM771 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM771 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM771 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM771 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30234] The complementary binding of VGAM771 RNA, herein designated VGAM RNA, to host target binding sites on VGAM771 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM771 host target RNA into VGAM771 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30235] It is appreciated that VGAM771 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM771 host target genes. The mRNA of each one of this plurality of VGAM771 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM771 RNA, herein designated VGAM RNA, and which when bound by VGAM771 RNA causes inhibition of translation of respective one or more VGAM771 host target proteins.

[30236] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM771 gene, herein designated VGAM GENE, on one or more VGAM771 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30237] It is yet further appreciated that a function of VGAM771 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM771 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM771 correlate with, and may be deduced from, the identity of the host target genes which VGAM771 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30238] Nucleotide sequences of the VGAM771 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM771 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM771 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM771 are further described hereinbelow with reference to Table 1.

[30239] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM771 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM771 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30240] As mentioned hereinabove with reference to Fig. 1, a function of VGAM771 gene, herein designated VGAM is inhibition of expression of VGAM771 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM771 correlate with, and may be deduced from, the identity of the target genes which VGAM771 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30241] Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_000109) is a VGAM771 host target gene. DMD BINDING SITE1 through DMD BINDING SITE13 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DMD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DMD BINDING SITE1 through DMD BINDING SITE13, designated SEQ ID:5569, SEQ ID:10154, SEQ ID:10159, SEQ ID:10166, SEQ

ID:10172, SEQ ID:10180, SEQ ID:10185, SEQ ID:10191, SEQ ID:10202, SEQ ID:10207, SEQ ID:10212, SEQ ID:10218 and SEQ ID:10230 respectively, to the nucleotide sequence of VGAM771 RNA, herein designated VGAM RNA, also designated SEQ ID:3482.

[30242] A function of VGAM771 is therefore inhibition of Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_000109), a gene which muscular dystrophy . Accordingly, utilities of VGAM771 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DMD. The function of DMD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM218.KIAA1219 (Accession XM\_028835) is another VGAM771 host target gene. KIAA1219 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1219, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1219 BINDING SITE, designated SEQ ID:30755, to the nucleotide sequence of VGAM771 RNA, herein designated

VGAM RNA, also designated SEQ ID:3482.

[30243] Another function of VGAM771 is therefore inhibition of KIAA1219 (Accession XM\_028835). Accordingly, utilities of VGAM771 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1219. LOC92979 (Accession NM\_138396) is another VGAM771 host target gene. LOC92979 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92979, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92979 BINDING SITE, designated SEQ ID:28764, to the nucleotide sequence of VGAM771 RNA, herein designated VGAM RNA, also designated SEQ ID:3482.

[30244] Another function of VGAM771 is therefore inhibition of LOC92979 (Accession NM\_138396). Accordingly, utilities of VGAM771 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92979. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 772 (VGAM772) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30245] VGAM772 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM772 was detected is described hereinabove with reference to Figs. 1–8.

[30246] VGAM772 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM772 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30247] VGAM772 gene encodes a VGAM772 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM772 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM772 precursor RNA is designated SEQ ID:758, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:758 is located at position 24433 relative to the genome of Bovine Coronavirus.

[30248] VGAM772 precursor RNA folds onto itself, forming



VGAM772 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30249] An enzyme complex designated DICER COMPLEX, `dices` the VGAM772 folded precursor RNA into VGAM772 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 49%) nucleotide sequence of VGAM772 RNA is designated SEQ ID:3483, and is provided hereinbelow with reference to the sequence listing part.

[30250] VGAM772 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM772 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM772 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30251] VGAM772 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM772 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM772 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM772 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM772 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30252] The complementary binding of VGAM772 RNA, herein designated VGAM RNA, to host target binding sites on VGAM772 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM772 host target RNA into VGAM772 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30253] It is appreciated that VGAM772 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM772 host target genes. The mRNA of each one of this plurality of VGAM772 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM772 RNA, herein designated VGAM RNA, and which when bound by VGAM772 RNA causes inhibition of translation of respective one or more VGAM772 host target proteins.

[30254] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM772 gene, herein designated VGAM GENE, on one or more VGAM772 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30255] It is yet further appreciated that a function of VGAM772 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM772 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM772 correlate with, and may be deduced from, the identity of the host target genes which VGAM772 binds and inhibits, and the

function of these host target genes, as elaborated herein–below.

[30256] Nucleotide sequences of the VGAM772 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM772 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM772 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM772 are further described hereinbelow with reference to Table 1.

[30257] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM772 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM772 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30258] As mentioned hereinabove with reference to Fig. 1, a function of VGAM772 gene, herein designated VGAM is inhibition of expression of VGAM772 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM772 correlate with, and may be deduced from, the identity of the target genes which VGAM772 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[30259] FLJ10178 (Accession NM\_018015) is a VGAM772 host target gene. FLJ10178 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10178, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10178 BINDING SITE, designated SEQ ID:19755, to the nucleotide sequence of VGAM772 RNA, herein designated VGAM RNA, also designated SEQ ID:3483.

[30260] A function of VGAM772 is therefore inhibition of FLJ10178 (Accession NM\_018015). Accordingly, utilities of VGAM772 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10178. LOC158014 (Accession XM\_088442) is another VGAM772 host target gene. LOC158014 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158014 BINDING SITE, designated SEQ ID:39695, to the nucleotide se-

quence of VGAM772 RNA, herein designated VGAM RNA, also designated SEQ ID:3483.

[30261] Another function of VGAM772 is therefore inhibition of LOC158014 (Accession XM\_088442). Accordingly, utilities of VGAM772 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158014. LOC255231 (Accession XM\_170908) is another VGAM772 host target gene. LOC255231 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255231, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255231 BINDING SITE, designated SEQ ID:45670, to the nucleotide sequence of VGAM772 RNA, herein designated VGAM RNA, also designated SEQ ID:3483.

[30262] Another function of VGAM772 is therefore inhibition of LOC255231 (Accession XM\_170908). Accordingly, utilities of VGAM772 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255231. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 773 (VGAM773) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30263] VGAM773 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM773 was detected is described hereinabove with reference to Figs. 1–8.

[30264] VGAM773 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM773 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30265] VGAM773 gene encodes a VGAM773 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM773 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM773 precursor RNA is designated SEQ ID:759, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:759 is located at position 23974 relative to the genome of Bovine Coronavirus.



[30266] VGAM773 precursor RNA folds onto itself, forming VGAM773 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30267] An enzyme complex designated DICER COMPLEX, `dices` the VGAM773 folded precursor RNA into VGAM773 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM773 RNA is designated SEQ ID:3484, and is provided hereinbelow with reference to the sequence listing part.

[30268] VGAM773 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM773 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM773 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30269] VGAM773 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM773 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM773 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM773 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM773 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30270] The complementary binding of VGAM773 RNA, herein designated VGAM RNA, to host target binding sites on VGAM773 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM773 host target RNA into VGAM773 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30271] It is appreciated that VGAM773 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM773 host target genes. The mRNA of each one of this plurality of VGAM773 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM773 RNA, herein designated VGAM RNA, and which when bound by VGAM773 RNA causes inhibition of translation of respective one or more VGAM773 host target proteins.

[30272] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM773 gene, herein designated VGAM GENE, on one or more VGAM773 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30273] It is yet further appreciated that a function of VGAM773 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM773 correlate with, and may be deduced from, the identity of the host

target genes which VGAM773 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30274] Nucleotide sequences of the VGAM773 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM773 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM773 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM773 are further described hereinbelow with reference to Table 1.

[30275] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM773 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM773 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30276] As mentioned hereinabove with reference to Fig. 1, a function of VGAM773 gene, herein designated VGAM is inhibition of expression of VGAM773 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM773 correlate with, and may be deduced from, the identity of the target genes which VGAM773

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30277] Fanconi Anemia, Complementation Group F (FANCF, Accession NM\_022725) is a VGAM773 host target gene. FANCF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FANCF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FANCF BINDING SITE, designated SEQ ID:22926, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30278] A function of VGAM773 is therefore inhibition of Fanconi Anemia, Complementation Group F (FANCF, Accession NM\_022725). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FANCF. NCK-associated Protein 1 (NCKAP1, Accession NM\_013436) is another VGAM773 host target gene. NCKAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCKAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCKAP1 BINDING SITE, designated SEQ ID:15097, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30279] Another function of VGAM773 is therefore inhibition of NCK-associated Protein 1 (NCKAP1, Accession NM\_013436). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCKAP1. Spinocerebellar Ataxia 7 (olivopontocerebellar atrophy with retinal degeneration) (SCA7, Accession NM\_000333) is another VGAM773 host target gene. SCA7 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SCA7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCA7 BINDING SITE, designated SEQ ID:5887, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30280] Another function of VGAM773 is therefore inhibition of Spinocerebellar Ataxia 7 (olivopontocerebellar atrophy

with retinal degeneration) (SCA7, Accession NM\_000333). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCA7. FLJ11259 (Accession NM\_018370) is another VGAM773 host target gene. FLJ11259 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11259, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11259 BINDING SITE, designated SEQ ID:20388, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30281] Another function of VGAM773 is therefore inhibition of FLJ11259 (Accession NM\_018370). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11259. FLJ20139 (Accession NM\_017685) is another VGAM773 host target gene. FLJ20139 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20139, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of FLJ20139 BINDING SITE, designated SEQ ID:19237, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30282] Another function of VGAM773 is therefore inhibition of FLJ20139 (Accession NM\_017685). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20139. KIAA0853 (Accession NM\_015070) is another VGAM773 host target gene. KIAA0853 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0853, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0853 BINDING SITE, designated SEQ ID:17439, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30283] Another function of VGAM773 is therefore inhibition of KIAA0853 (Accession NM\_015070). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0853. KIAA1189 (Accession XM\_050508) is another

VGAM773 host target gene. KIAA1189 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1189, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1189 BINDING SITE, designated SEQ ID:35654, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30284] Another function of VGAM773 is therefore inhibition of KIAA1189 (Accession XM\_050508). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1189. KIAA1423 (Accession XM\_029703) is another VGAM773 host target gene. KIAA1423 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1423 BINDING SITE, designated SEQ ID:30924, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30285] Another function of VGAM773 is therefore inhibition of KIAA1423 (Accession XM\_029703). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1423. LOC143879 (Accession XM\_084666) is another VGAM773 host target gene. LOC143879 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143879, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143879 BINDING SITE, designated SEQ ID:37663, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30286] Another function of VGAM773 is therefore inhibition of LOC143879 (Accession XM\_084666). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143879. LOC152905 (Accession XM\_017966) is another VGAM773 host target gene. LOC152905 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152905, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152905 BINDING SITE, designated SEQ ID:30333, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30287] Another function of VGAM773 is therefore inhibition of LOC152905 (Accession XM\_017966). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152905. LOC170395 (Accession XM\_084325) is another VGAM773 host target gene. LOC170395 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC170395, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC170395 BINDING SITE, designated SEQ ID:37547, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30288] Another function of VGAM773 is therefore inhibition of LOC170395 (Accession XM\_084325). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC170395. LOC200268 (Accession XM\_114178) is another VGAM773 host target gene. LOC200268 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200268 BINDING SITE, designated SEQ ID:42764, to the nucleotide sequence of VGAM773 RNA, herein designated VGAM RNA, also designated SEQ ID:3484.

[30289] Another function of VGAM773 is therefore inhibition of LOC200268 (Accession XM\_114178). Accordingly, utilities of VGAM773 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200268. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 774 (VGAM774) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30290] VGAM774 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM774 was detected is described hereinabove with reference to Figs. 1–8.

[30291] VGAM774 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus.

VGAM774 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30292] VGAM774 gene encodes a VGAM774 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM774 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM774 precursor RNA is designated SEQ ID:760, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:760 is located at position 23642 relative to the genome of Bovine Coronavirus.

[30293] VGAM774 precursor RNA folds onto itself, forming VGAM774 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30294] An enzyme complex designated DICER COMPLEX, `dices` the VGAM774 folded precursor RNA into VGAM774 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM774 RNA is designated SEQ ID:3485, and is provided hereinbelow with reference to the sequence listing part.

[30295] VGAM774 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM774 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM774 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30296] VGAM774 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM774 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM774 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM774 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM774 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[30297] The complementary binding of VGAM774 RNA, herein designated VGAM RNA, to host target binding sites on



VGAM774 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM774 host target RNA into VGAM774 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30298] It is appreciated that VGAM774 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM774 host target genes. The mRNA of each one of this plurality of VGAM774 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM774 RNA, herein designated VGAM RNA, and which when bound by VGAM774 RNA causes inhibition of translation of respective one or more VGAM774 host target proteins.

[30299] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM774 gene, herein designated VGAM GENE, on one or more VGAM774 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30300] It is yet further appreciated that a function of VGAM774 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM774 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM774 correlate with, and may be deduced from, the identity of the host target genes which VGAM774 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30301] Nucleotide sequences of the VGAM774 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM774 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM774 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM774 are further described hereinbelow with reference to Table 1.

[30302] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM774 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM774 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30303] As mentioned hereinabove with reference to Fig. 1, a function of VGAM774 gene, herein designated VGAM is inhibition of expression of VGAM774 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM774 correlate with, and may be deduced from, the identity of the target genes which VGAM774 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30304] Eukaryotic Translation Initiation Factor 1A (EIF1A, Accession XM\_114147) is a VGAM774 host target gene. EIF1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF1A, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF1A BINDING SITE, designated SEQ ID:42724, to the nucleotide sequence of VGAM774 RNA, herein designated VGAM RNA, also designated SEQ ID:3485.

[30305] A function of VGAM774 is therefore inhibition of Eukaryotic Translation Initiation Factor 1A (EIF1A, Accession XM\_114147), a gene which seems to be required for maximal rate of protein biosynthesis. Accordingly, utilities of VGAM774 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF1A. The function of EIF1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM120. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 775 (VGAM775) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30306] VGAM775 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM775 was detected is described hereinabove with reference to Figs. 1–8.

[30307] VGAM775 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Coronavirus. VGAM775 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30308] VGAM775 gene encodes a VGAM775 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM775 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM775 precursor RNA is designated SEQ ID:761, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:761 is located at position 24623 relative to the genome of Bovine Coronavirus.

[30309] VGAM775 precursor RNA folds onto itself, forming VGAM775 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30310] An enzyme complex designated DICER COMPLEX, `dices` the VGAM775 folded precursor RNA into VGAM775 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM775 RNA is designated SEQ ID:3486, and is provided hereinbelow with reference to the sequence listing part.

[30311] VGAM775 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM775 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM775 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30312] VGAM775 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM775 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM775 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM775 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM775 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30313] The complementary binding of VGAM775 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM775 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM775 host target RNA into VGAM775 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30314] It is appreciated that VGAM775 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM775 host target genes. The mRNA of each one of this plurality of VGAM775 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM775 RNA, herein designated VGAM RNA, and which when bound by VGAM775 RNA causes inhibition of translation of respective one or more VGAM775 host target proteins.

[30315] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM775 gene, herein designated VGAM GENE, on one or more VGAM775 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other



known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30316] It is yet further appreciated that a function of VGAM775 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM775 include diagnosis, prevention and treatment of viral infection by Bovine Coronavirus. Specific functions, and accordingly utilities, of VGAM775 correlate with, and may be deduced from, the identity of the host target genes which VGAM775 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30317] Nucleotide sequences of the VGAM775 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM775 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM775 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM775 are further described hereinbelow with reference to Table 1.

[30318] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM775 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM775 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30319] As mentioned hereinabove with reference to Fig. 1, a function of VGAM775 gene, herein designated VGAM is inhibition of expression of VGAM775 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM775 correlate with, and may be deduced from, the identity of the target genes which VGAM775 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30320] Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362) is a VGAM775 host target gene. TIMP3 BIND-

ING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TIMP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMP3 BINDING SITE, designated SEQ ID:5926, to the nucleotide sequence of VGAM775 RNA, herein designated VGAM RNA, also designated SEQ ID:3486.

[30321] A function of VGAM775 is therefore inhibition of Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362). Accordingly, utilities of VGAM775 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIMP3. LOC90785 (Accession XM\_034110) is another VGAM775 host target gene. LOC90785 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC90785, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90785 BINDING SITE, designated SEQ ID:32006, to the nucleotide sequence of VGAM775 RNA, herein designated VGAM RNA, also designated SEQ ID:3486.

[30322] Another function of VGAM775 is therefore inhibition of LOC90785 (Accession XM\_034110). Accordingly, utilities of VGAM775 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90785. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 776 (VGAM776) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30323] VGAM776 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM776 was detected is described hereinabove with reference to Figs. 1–8.

[30324] VGAM776 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Culex Nigripalpus Baculovirus. VGAM776 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30325] VGAM776 gene encodes a VGAM776 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM776

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM776 precursor RNA is designated SEQ ID:762, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:762 is located at position 29557 relative to the genome of Culex Nigripalpus Baculovirus.

[30326] VGAM776 precursor RNA folds onto itself, forming VGAM776 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30327] An enzyme complex designated DICER COMPLEX, `dices` the VGAM776 folded precursor RNA into VGAM776 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 83%) nucleotide sequence of VGAM776 RNA is designated SEQ ID:3487, and is provided hereinbelow with reference to the sequence listing part.

[30328] VGAM776 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM776 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM776 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[30329] VGAM776 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM776 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM776 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM776 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM776 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30330] The complementary binding of VGAM776 RNA, herein designated VGAM RNA, to host target binding sites on VGAM776 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM776 host target RNA into VGAM776 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30331] It is appreciated that VGAM776 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM776 host target genes. The mRNA of each one of this plurality of VGAM776 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM776 RNA, herein designated VGAM RNA, and which when bound by VGAM776 RNA causes inhibition of translation of respective one or more VGAM776 host target proteins.

[30332] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM776 gene, herein designated VGAM GENE, on one or more VGAM776 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).



[30333] It is yet further appreciated that a function of VGAM776 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM776 include diagnosis, prevention and treatment of viral infection by Culex Nigripalpus Baculovirus. Specific functions, and accordingly utilities, of VGAM776 correlate with, and may be deduced from, the identity of the host target genes which VGAM776 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30334] Nucleotide sequences of the VGAM776 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM776 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM776 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM776 are further described hereinbelow with reference to Table 1.

[30335] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM776 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM776 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[30336] As mentioned hereinabove with reference to Fig. 1, a function of VGAM776 gene, herein designated VGAM is inhibition of expression of VGAM776 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM776 correlate with, and may be deduced from, the identity of the target genes which VGAM776 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30337] KIAA0826 (Accession XM\_093839) is a VGAM776 host target gene. KIAA0826 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0826 BINDING SITE, designated SEQ ID:40216, to the nucleotide sequence of VGAM776 RNA, herein designated VGAM RNA, also designated SEQ ID:3487.

[30338] A function of VGAM776 is therefore inhibition of KIAA0826 (Accession XM\_093839). Accordingly, utilities of VGAM776 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0826. MGC2654 (Accession NM\_024109) is another VGAM776 host target gene. MGC2654 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2654, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2654 BINDING SITE, designated SEQ ID:23554, to the nucleotide sequence of VGAM776 RNA, herein designated VGAM RNA, also designated SEQ ID:3487.

[30339] Another function of VGAM776 is therefore inhibition of MGC2654 (Accession NM\_024109). Accordingly, utilities of VGAM776 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2654. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 777 (VGAM777) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30340] VGAM777 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM777 was detected is described hereinabove with reference to Figs. 1–8.

[30341] VGAM777 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Culex Nigripalpus Baculovirus. VGAM777 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30342] VGAM777 gene encodes a VGAM777 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM777 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM777 precursor RNA is designated SEQ ID:763, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:763 is located at position 71215 relative to the genome of Culex Nigripalpus Baculovirus.

[30343] VGAM777 precursor RNA folds onto itself, forming VGAM777 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30344] An enzyme complex designated DICER COMPLEX, `dices` the VGAM777 folded precursor RNA into VGAM777 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM777 RNA is designated SEQ ID:3488, and is provided hereinbelow with reference to the sequence listing part.

[30345] VGAM777 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM777 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM777 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30346] VGAM777 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM777 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM777 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM777 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM777 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[30347] The complementary binding of VGAM777 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM777 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM777 host target RNA into VGAM777 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30348] It is appreciated that VGAM777 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM777 host target genes. The mRNA of each one of this plurality of VGAM777 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM777 RNA, herein designated VGAM RNA, and which when bound by VGAM777 RNA causes inhibition of translation of respective one or more VGAM777 host target proteins.

[30349] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM777 gene, herein designated VGAM GENE, on one or more VGAM777 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30350] It is yet further appreciated that a function of VGAM777 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of viral infection by Culex Nigripalpus Baculovirus. Specific functions, and accordingly utilities, of VGAM777 correlate with, and may be deduced from, the identity of the host target genes which VGAM777 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30351] Nucleotide sequences of the VGAM777 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM777 RNA, herein designated VGAM RNA,



and a schematic representation of the secondary folding of VGAM777 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM777 are further described hereinbelow with reference to Table 1.

[30352] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM777 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM777 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30353] As mentioned hereinabove with reference to Fig. 1, a function of VGAM777 gene, herein designated VGAM is inhibition of expression of VGAM777 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM777 correlate with, and may be deduced from, the identity of the target genes which VGAM777 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30354] Ankyrin 1, Erythrocytic (ANK1, Accession XM\_016774) is a VGAM777 host target gene. ANK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ANK1, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANK1 BINDING SITE, designated SEQ ID:30288, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30355] A function of VGAM777 is therefore inhibition of Ankyrin 1, Erythrocytic (ANK1, Accession XM\_016774). Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANK1. Glycogenin (GYG, Accession NM\_004130) is another VGAM777 host target gene. GYG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GYG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GYG BINDING SITE, designated SEQ ID:10339, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30356] Another function of VGAM777 is therefore inhibition of Glycogenin (GYG, Accession NM\_004130), a gene which primes de novo glycogen synthesis. Accordingly, utilities

of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GYG. The function of GYG has been established by previous studies. Glycogenin is a self-glucosylating protein involved in the initiation reactions of glycogen synthesis. During initiation, the covalent attachment of a glucose residue to glycogenin is followed by elongation to form an oligosaccharide chain. Viskupic et al. (1992) isolated cDNAs encoding glycogenin from rabbit muscle, rat, and cow. Recombinant mammalian glycogenin was enzymatically active and capable of self-glucosylation. After incubation with UDP-glucose, the recombinant protein was able to serve as a substrate for glycogen synthase, leading to the production of high M(r) polysaccharide. Barbetti et al. (1996) identified a human glycogenin cDNA. The predicted 333-amino acid human protein shares 93% identity with rabbit muscle glycogenin. Northern blot analysis revealed that the 2.4-kb glycogenin mRNA was expressed prominently in human skeletal muscle and heart, and to a lesser extent in several other tissues. Mu et al. (1997) isolated cDNAs encoding a related protein, which they designated glycogenin-2 (OMIM Ref. No. 300198). They suggested that muscle glycogenin be referred to as glyco-

genin-1.

[30357] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30358] Barbetti, F.; Rocchi, M.; Bossolasco, M.; Cordera, R.; Sbraccia, P.; Finelli, P.; Consalez, G. G. : The human skeletal muscle glycogenin gene: cDNA, tissue expression, and chromosomal localization. *Biochem. Biophys. Res. Commun.* 220: 72-77, 1996. ; and

[30359] Mu, J.; Skurat, A. V.; Roach, P. J. : Glycogenin-2, a novel self-glucosylating protein involved in liver glycogen biosynthesis. *J. Biol. Chem.* 272: 27589-27597, 1997.

[30360] Further studies establishing the function and utilities of GYG are found in John Hopkins OMIM database record ID 603942, and in cited publications numbered 5043, 518 and 11401 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Heterogeneous Nuclear Ribonucleoprotein F (HNRPF, Accession NM\_004966) is another VGAM777 host target gene. HNRPF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HNRPF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of HNRPF BINDING SITE, designated SEQ ID:11414, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30361] Another function of VGAM777 is therefore inhibition of Heterogeneous Nuclear Ribonucleoprotein F (HNRPF, Accession NM\_004966). Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HNRPF. inositol(myo)-1(or 4)-monophosphatase 2 (IMPA2, Accession XM\_170862) is another VGAM777 host target gene. IMPA2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by IMPA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IMPA2 BINDING SITE, designated SEQ ID:45631, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30362] Another function of VGAM777 is therefore inhibition of inositol(myo)-1(or 4)-monophosphatase 2 (IMPA2, Accession XM\_170862). Accordingly, utilities of VGAM777 in-

clude diagnosis, prevention and treatment of diseases and clinical conditions associated with IMPA2. MAD, Mothers Against Decapentaplegic Homolog 4 (Drosophila) (MADH4, Accession NM\_005359) is another VGAM777 host target gene. MADH4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MADH4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MADH4 BINDING SITE, designated SEQ ID:11830, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30363] Another function of VGAM777 is therefore inhibition of MAD, Mothers Against Decapentaplegic Homolog 4 (Drosophila) (MADH4, Accession NM\_005359), a gene which common mediator of signal transduction by  $\text{tgf-}\beta$  (transforming growth factor) superfamily; smad4 is the common smad (co-smad). promotes binding of the smad2/smad4/fast-1 complex to dna and provides an activation function required for smad1 or smad2 to stimulate transcription. may act as a tumor suppressor. Accordingly, utilities of VGAM777 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with MADH4. The function of MADH4 and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM217. Ribosomal Protein S6 Kinase, 90kDa, Polypeptide 5 (RPS6KA5, Accession NM\_004755) is another VGAM777 host target gene. RPS6KA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RPS6KA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RPS6KA5 BINDING SITE, designated SEQ ID:11143, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30364] Another function of VGAM777 is therefore inhibition of Ribosomal Protein S6 Kinase, 90kDa, Polypeptide 5 (RPS6KA5, Accession NM\_004755), a gene which plays an essential role in the proliferation of yeast cells. Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RPS6KA5. The function of RPS6KA5 and its asso-

ciation with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM191.FLJ20519 (Accession NM\_017860) is another VGAM777 host target gene.

FLJ20519 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20519 BINDING SITE, designated SEQ ID:19536, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30365] Another function of VGAM777 is therefore inhibition of FLJ20519 (Accession NM\_017860). Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20519. HSPC072 (Accession NM\_014162) is another VGAM777 host target gene. HSPC072 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HSPC072, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity



of the nucleotide sequences of HSPC072 BINDING SITE, designated SEQ ID:15460, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30366] Another function of VGAM777 is therefore inhibition of HSPC072 (Accession NM\_014162). Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC072. KIAA0678 (Accession XM\_039828) is another VGAM777 host target gene. KIAA0678 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0678, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0678 BINDING SITE, designated SEQ ID:33196, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30367] Another function of VGAM777 is therefore inhibition of KIAA0678 (Accession XM\_039828). Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0678. Zinc Finger, DHHC Domain Containing 5

(ZDHHC5, Accession XM\_166204) is another VGAM777 host target gene. ZDHHC5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ZDHHC5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZDHHC5 BINDING SITE, designated SEQ ID:44007, to the nucleotide sequence of VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30368] Another function of VGAM777 is therefore inhibition of Zinc Finger, DHHC Domain Containing 5 (ZDHHC5, Accession XM\_166204). Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZDHHC5. LOC199990 (Accession XM\_114083) is another VGAM777 host target gene. LOC199990 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC199990, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199990 BINDING SITE, designated SEQ ID:42679, to the nucleotide sequence of

VGAM777 RNA, herein designated VGAM RNA, also designated SEQ ID:3488.

[30369] Another function of VGAM777 is therefore inhibition of LOC199990 (Accession XM\_114083). Accordingly, utilities of VGAM777 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199990. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 778 (VGAM778) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30370] VGAM778 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM778 was detected is described hereinabove with reference to Figs. 1–8.

[30371] VGAM778 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Culex Nigripalpus Baculovirus. VGAM778 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30372] VGAM778 gene encodes a VGAM778 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM778 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM778 precursor RNA is designated SEQ ID:764, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:764 is located at position 84607 relative to the genome of Culex Nigripalpus Baculovirus.

[30373] VGAM778 precursor RNA folds onto itself, forming VGAM778 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30374] An enzyme complex designated DICER COMPLEX, `dices` the VGAM778 folded precursor RNA into VGAM778 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 86%) nucleotide sequence of VGAM778 RNA is designated SEQ ID:3489, and is provided hereinbelow with reference to the sequence listing part.

[30375] VGAM778 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM778 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM778 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30376] VGAM778 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM778 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM778 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM778 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM778 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30377] The complementary binding of VGAM778 RNA, herein designated VGAM RNA, to host target binding sites on VGAM778 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM778 host target RNA into VGAM778 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30378] It is appreciated that VGAM778 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM778 host target genes. The mRNA of each one of this plurality of VGAM778 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM778 RNA, herein designated VGAM RNA, and which when bound by VGAM778 RNA causes inhibition of translation of respective one or more VGAM778 host target proteins.

[30379] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM778 gene, herein designated VGAM GENE, on one or more VGAM778 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[30380] It is yet further appreciated that a function of VGAM778 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of viral infection by Culex Nigripalpus Baculovirus. Specific functions, and accordingly utilities, of VGAM778 correlate with, and may be deduced from, the identity of the host target genes which VGAM778 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30381] Nucleotide sequences of the VGAM778 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM778 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM778 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM778 are further described hereinbelow with reference to Table 1.

[30382] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM778 host target RNA, and schematic representation of the complementarity of each of these



host target binding sites to VGAM778 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30383] As mentioned hereinabove with reference to Fig. 1, a function of VGAM778 gene, herein designated VGAM is inhibition of expression of VGAM778 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM778 correlate with, and may be deduced from, the identity of the target genes which VGAM778 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30384] Nucleoporin 98kDa (NUP98, Accession NM\_016320) is a VGAM778 host target gene. NUP98 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUP98, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUP98 BINDING SITE, designated SEQ ID:18440, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30385] A function of VGAM778 is therefore inhibition of Nucleoporin 98kDa (NUP98, Accession NM\_016320), a gene

which functions in the nuclear transport of protein and RNA. Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUP98. The function of NUP98 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM55. Oxytocin Receptor (OXTR, Accession NM\_000916) is another VGAM778 host target gene. OXTR BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by OXTR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OXTR BINDING SITE, designated SEQ ID:6620, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30386] Another function of VGAM778 is therefore inhibition of Oxytocin Receptor (OXTR, Accession NM\_000916), a gene which induces inward ion currents. Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OXTR. The function of OXTR and its association with various diseases

and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM636.PR1 (Accession XM\_056490) is another VGAM778 host target gene. PR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PR1 BINDING SITE, designated SEQ ID:36399, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30387] Another function of VGAM778 is therefore inhibition of PR1 (Accession XM\_056490), a gene which may function as a hematopoietic receptor. Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PR1. The function of PR1 has been established by previous studies. Using subtractive hybridization of mRNA from polycythemia vera (OMIM Ref. No. 263300) patient granulocytes and mRNA from normal granulocytes, Temerinac et al. (2000) isolated a cDNA encoding NB1, which they called PR1. Northern blot analysis revealed expression of

2.1- and 3.1-kb transcripts in granulocytes from PV patients but not normal granulocytes. Weak expression of PRV1 was seen in a patient with idiopathic myelofibrosis (see OMIM Ref. No. 254450) and in some patients with essential thrombocythemia (see OMIM Ref. No. 187950), but no expression was seen in patients with acute or chronic myelogenous leukemia (see OMIM Ref. No. 601626 and 151410, respectively) or in patients with polycythemic secondary erythrocytosis. Strong expression in bone marrow and slight expression in fetal liver was detected, but PRV1 was not expressed in other tissues. Treatment of normal stem cell donors or, in vitro, normal granulocytes, with GCSF (CSF3; 138970) or CSF2 (OMIM Ref. No. 138960) induced expression initially of the 3.1-kb transcript and, subsequently, the 2.1 kb transcript. The deduced 437-amino acid PRV1 protein contains an N-terminal signal sequence, 2 highly homologous 188-residue cysteine-rich domains that share homology with UPAR domains (see OMIM Ref. No. 606119), and a highly hydrophobic C-terminal sequence probably encoding a GPI link. Western blot and flow cytometric analyses showed cell surface expression of a 60-kD protein, 14 kD greater than the predicted size, probably due to the pres-

ence of 3 potential N-glycosylation sites. Immunohistochemistry demonstrated expression in bone marrow early erythroblasts, megakaryocytes, promyelocytes, and myelocytes. Independently, Kissel et al. (2001) cloned and characterized NB1, which they also referred to as CD177 and HNA2A. They obtained the cDNA after purification and microsequence analysis of NB1 protein from normal resting granulocytes. Kissel et al. (2001) noted amino acid differences between the PRV1 (Temerinac et al., 2000) and NB1 sequences at positions 3, 119, 323, and 379 and suggested that 2 different, highly homologous genes may exist. By genomic sequence analysis and PCR, Kissel et al. (2002) determined that the NB1 gene contains 9 exons. By genomic sequence analysis, Kissel et al. (2001) mapped the NB1 gene to chromosome 19q13.2. Kissel et al. (2002) reported that 2 women with no cell-surface NB1 expression but with NB1-specific alloantibodies after delivery of babies with alloimmune neonatal neutropenia possessed genomic NB1. The authors determined that the NB1-negative phenotype resulted from different off-frame insertions at the RNA level causing an absence of GPI linkage sites and transmembrane segments. Kissel et al. (2002) concluded that any putative soluble fragments

produced were unable to prevent alloimmunization.

[30388] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30389] Kissel, K.; Santoso, S.; Hofmann, C.; Stroncek, D.; Bux, J. : Molecular basis of the neutrophil glycoprotein NB1 (CD177) involved in the pathogenesis of immune neutropenias and transfusion reactions. *Europ. J. Immun.* 31: 1301–1309, 2001. ; and

[30390] Kissel, K.; Scheffler, S.; Kerowgan, M.; Bux, J. : Molecular basis of NB1 (HNA–2a, CD177) deficiency. *Blood* 99: 4231–4233, 2002.

[30391] Further studies establishing the function and utilities of PRV1 are found in John Hopkins OMIM database record ID 162860, and in cited publications numbered 693–696 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362) is another VGAM778 host target gene. TIMP3 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by TIMP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMP3 BINDING SITE, designated SEQ ID:5928, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30392] Another function of VGAM778 is therefore inhibition of Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIMP3. CLONE24945 (Accession NM\_015683) is another VGAM778 host target gene. CLONE24945 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLONE24945, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLONE24945 BINDING SITE, designated SEQ ID:17905, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30393] Another function of VGAM778 is therefore inhibition of CLONE24945 (Accession NM\_015683). Accordingly, utili-

ties of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLONE24945. HUMAGCGB (Accession NM\_013286) is another VGAM778 host target gene. HUMAGCGB BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HUMAGCGB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HUMAGCGB BINDING SITE, designated SEQ ID:14956, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30394] Another function of VGAM778 is therefore inhibition of HUMAGCGB (Accession NM\_013286). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUMAGCGB. KIAA0062 (Accession XM\_046677) is another VGAM778 host target gene. KIAA0062 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0062, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of



KIAA0062 BINDING SITE, designated SEQ ID:34794, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30395] Another function of VGAM778 is therefore inhibition of KIAA0062 (Accession XM\_046677). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0062. MGC4737 (Accession NM\_031466) is another VGAM778 host target gene. MGC4737 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC4737, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4737 BINDING SITE, designated SEQ ID:25508, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30396] Another function of VGAM778 is therefore inhibition of MGC4737 (Accession NM\_031466). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4737. LOC118611 (Accession XM\_061055) is another VGAM778 host target gene. LOC118611 BINDING SITE is

HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC118611, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC118611 BINDING SITE, designated SEQ ID:37188, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30397] Another function of VGAM778 is therefore inhibition of LOC118611 (Accession XM\_061055). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC118611. LOC146880 (Accession XM\_085627) is another VGAM778 host target gene. LOC146880 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC146880, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146880 BINDING SITE, designated SEQ ID:38261, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30398] Another function of VGAM778 is therefore inhibition of

LOC146880 (Accession XM\_085627). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146880. LOC148811 (Accession XM\_086326) is another VGAM778 host target gene. LOC148811 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148811, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148811 BINDING SITE, designated SEQ ID:38600, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30399] Another function of VGAM778 is therefore inhibition of LOC148811 (Accession XM\_086326). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148811. LOC150605 (Accession XM\_097927) is another VGAM778 host target gene. LOC150605 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150605, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC150605 BINDING SITE, designated SEQ ID:41229, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30400] Another function of VGAM778 is therefore inhibition of LOC150605 (Accession XM\_097927). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150605. LOC152065 (Accession XM\_098159) is another VGAM778 host target gene. LOC152065 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152065, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152065 BINDING SITE, designated SEQ ID:41429, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30401] Another function of VGAM778 is therefore inhibition of LOC152065 (Accession XM\_098159). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152065. LOC221300 (Accession XM\_166322) is an-

other VGAM778 host target gene. LOC221300 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221300, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221300 BINDING SITE, designated SEQ ID:44147, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30402] Another function of VGAM778 is therefore inhibition of LOC221300 (Accession XM\_166322). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221300. LOC221895 (Accession XM\_166511) is another VGAM778 host target gene. LOC221895 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221895 BINDING SITE, designated SEQ ID:44445, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30403] Another function of VGAM778 is therefore inhibition of LOC221895 (Accession XM\_166511). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221895. LOC90170 (Accession XM\_029589) is another VGAM778 host target gene. LOC90170 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90170 BINDING SITE, designated SEQ ID:30906, to the nucleotide sequence of VGAM778 RNA, herein designated VGAM RNA, also designated SEQ ID:3489.

[30404] Another function of VGAM778 is therefore inhibition of LOC90170 (Accession XM\_029589). Accordingly, utilities of VGAM778 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90170. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 779 (VGAM779) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[30405] VGAM779 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM779 was detected is described hereinabove with reference to Figs. 1–8.

[30406] VGAM779 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Spodoptera Litura Nucleopolyhedrovirus. VGAM779 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30407] VGAM779 gene encodes a VGAM779 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM779 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM779 precursor RNA is designated SEQ ID:765, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:765 is located at position 23915 relative to the genome of Spodoptera Litura Nucleopolyhedrovirus.

[30408] VGAM779 precursor RNA folds onto itself, forming VGAM779 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[30409] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM779 folded precursor RNA into VGAM779 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 43%) nucleotide se-  
quence of VGAM779 RNA is designated SEQ ID:3490, and  
is provided hereinbelow with reference to the sequence  
listing part.

[30410] VGAM779 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM779 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM779 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding



gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30411] VGAM779 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM779 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM779 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM779 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM779 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30412] The complementary binding of VGAM779 RNA, herein designated VGAM RNA, to host target binding sites on VGAM779 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM779 host target RNA into VGAM779 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30413] It is appreciated that VGAM779 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM779 host target genes. The mRNA of each one of this plurality of VGAM779 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM779 RNA, herein designated VGAM RNA, and which when bound by VGAM779 RNA causes inhibition of translation of respective one or more VGAM779 host target proteins.

[30414] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM779 gene, herein designated VGAM GENE, on one or more VGAM779 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30415] It is yet further appreciated that a function of VGAM779 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM779 include diagnosis, prevention and treatment of viral infection by Spodoptera Litura Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM779 correlate with, and may be deduced from, the identity of the host target genes which VGAM779 binds and inhibits, and the function of these

host target genes, as elaborated hereinbelow.

[30416] Nucleotide sequences of the VGAM779 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM779 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM779 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM779 are further described hereinbelow with reference to Table 1.

[30417] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM779 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM779 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30418] As mentioned hereinabove with reference to Fig. 1, a function of VGAM779 gene, herein designated VGAM is inhibition of expression of VGAM779 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM779 correlate with, and may be deduced from, the identity of the target genes which VGAM779 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30419] Pentaxin-related Gene, Rapidly Induced By IL-1 Beta (PTX3, Accession NM\_002852) is a VGAM779 host target gene. PTX3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTX3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTX3 BINDING SITE, designated SEQ ID:8746, to the nucleotide sequence of VGAM779 RNA, herein designated VGAM RNA, also designated SEQ ID:3490.

[30420] A function of VGAM779 is therefore inhibition of Pentaxin-related Gene, Rapidly Induced By IL-1 Beta (PTX3, Accession NM\_002852), a gene which is similar to the pentaxin subclass of inflammatory acute-phase proteins. Accordingly, utilities of VGAM779 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTX3. The function of PTX3 has been established by previous studies. In a search for genes that can serve as markers of inflammatory reactions involving the vessel wall, Breviario et al. (1992) used differential hybridization to identify several cDNAs that are induced in human umbilical vein endothelial cells by interleukin-1-beta (IL1B; 147720). The only novel gene among these

cDNAs, named PTX3, encoded a predicted 381-amino acid protein with homology to the pentraxin protein family (see OMIM Ref. No. 600750). Based on the Greek derivation, Breviario et al. (1992) suggested that this family be named pentaxin. The PTX3 gene contains 3 exons and is transcribed as a 1,861-nucleotide mRNA. Breviario et al. (1992) mapped PTX3 to 3q25 using somatic cell hybrid analysis and fluorescence in situ hybridization. Basile et al. (1997) suggested that PTX3 belongs to the family of 'long pentraxins', which have C-terminal pentraxin domains and novel amino-terminal domains. They studied the PTX3 promoter and found a 1,317-bp fragment, located 5-prime to the transcriptional start site, that confers TNF- and IL1B-inducible transcriptional activity in transfected fibroblasts. They also identified a functional NF-kappa-B (164011, 164012) site in the promoter.

[30421] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30422] Basile, A.; Sica, A.; d'Aniello, E.; Breviario, F.; Garrido, G.; Castellano, M.; Mantovani, A.; Introna, M. : Characterization of the promoter for the human long pentraxin PTX3: role of NF-kappa-B in tumor necrosis factor-alpha and

interleukin-1-beta regulation. J. Biol. Chem. 272:  
8172-8178, 1997. ; and

[30423] Breviario, F.; d'Aniello, E. M.; Golay, J.; Peri, G.; Bottazzi, B.; Bairoch, A.; Saccone, S.; Marzella, R.; Predazzi, V.; Rocchi, M.; Della Valle, G.; Dejana, E.; Mantovani, A.; Introna.

[30424] Further studies establishing the function and utilities of PTX3 are found in John Hopkins OMIM database record ID 602492, and in cited publications numbered 103 and 8250-8251 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), Member 1 (SLC1A1, Accession NM\_004170) is another VGAM779 host target gene. SLC1A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC1A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC1A1 BINDING SITE, designated SEQ ID:10376, to the nucleotide sequence of VGAM779 RNA, herein designated VGAM RNA, also designated SEQ ID:3490.

[30425] Another function of VGAM779 is therefore inhibition of

Solute Carrier Family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), Member 1 (SLC1A1, Accession NM\_004170), a gene which is a glutamate transporter, essential for terminating the postsynaptic action of glutamate by rapidly removing it from the synaptic cleft. Accordingly, utilities of VGAM779 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC1A1. The function of SLC1A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM206.Potassium Channel, Subfamily V, Member 1 (KCNV1, Accession NM\_014379) is another VGAM779 host target gene. KCNV1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNV1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNV1 BINDING SITE, designated SEQ ID:15714, to the nucleotide sequence of VGAM779 RNA, herein designated VGAM RNA, also designated SEQ ID:3490.

[30426] Another function of VGAM779 is therefore inhibition of



Potassium Channel, Subfamily V, Member 1 (KCNV1, Accession NM\_014379). Accordingly, utilities of VGAM779 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNV1. KIAA1028 (Accession XM\_166324) is another VGAM779 host target gene. KIAA1028 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1028 BINDING SITE, designated SEQ ID:44153, to the nucleotide sequence of VGAM779 RNA, herein designated VGAM RNA, also designated SEQ ID:3490.

[30427] Another function of VGAM779 is therefore inhibition of KIAA1028 (Accession XM\_166324). Accordingly, utilities of VGAM779 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1028. LOC201203 (Accession XM\_113920) is another VGAM779 host target gene. LOC201203 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201203, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201203 BINDING SITE, designated SEQ ID:42536, to the nucleotide sequence of VGAM779 RNA, herein designated VGAM RNA, also designated SEQ ID:3490.

[30428] Another function of VGAM779 is therefore inhibition of LOC201203 (Accession XM\_113920). Accordingly, utilities of VGAM779 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201203. LOC221895 (Accession XM\_166511) is another VGAM779 host target gene. LOC221895 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221895 BINDING SITE, designated SEQ ID:44446, to the nucleotide sequence of VGAM779 RNA, herein designated VGAM RNA, also designated SEQ ID:3490.

[30429] Another function of VGAM779 is therefore inhibition of LOC221895 (Accession XM\_166511). Accordingly, utilities of VGAM779 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC221895. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 780 (VGAM780) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30430] VGAM780 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM780 was detected is described hereinabove with reference to Figs. 1–8.

[30431] VGAM780 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Spodoptera Litura Nucleopolyhedrovirus. VGAM780 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30432] VGAM780 gene encodes a VGAM780 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM780 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM780 precursor RNA is designated SEQ ID:766, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:766 is located at position 95927 relative to the genome of Spodoptera Litura Nucleopolyhedrovirus.

[30433] VGAM780 precursor RNA folds onto itself, forming VGAM780 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30434] An enzyme complex designated DICER COMPLEX, `dices` the VGAM780 folded precursor RNA into VGAM780 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 72%) nucleotide sequence of VGAM780 RNA is designated SEQ ID:3491, and is provided hereinbelow with reference to the sequence listing part.

[30435] VGAM780 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM780 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM780 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30436] VGAM780 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM780 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM780 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM780 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM780 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[30437] The complementary binding of VGAM780 RNA, herein designated VGAM RNA, to host target binding sites on VGAM780 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM780 host target RNA into VGAM780 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30438] It is appreciated that VGAM780 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM780 host target genes. The mRNA of each one of this plurality of VGAM780 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM780 RNA, herein designated VGAM RNA, and which when bound by VGAM780 RNA causes in-

hibition of translation of respective one or more VGAM780 host target proteins.

[30439] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM780 gene, herein designated VGAM GENE, on one or more VGAM780 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30440] It is yet further appreciated that a function of VGAM780 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM780 include diagnosis, prevention and

treatment of viral infection by Spodoptera Litura Nucleopolyhedrovirus. Specific functions, and accordingly utilities, of VGAM780 correlate with, and may be deduced from, the identity of the host target genes which VGAM780 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30441] Nucleotide sequences of the VGAM780 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM780 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM780 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM780 are further described hereinbelow with reference to Table 1.

[30442] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM780 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM780 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30443] As mentioned hereinabove with reference to Fig. 1, a function of VGAM780 gene, herein designated VGAM is inhibition of expression of VGAM780 target genes. It is



appreciated that specific functions, and accordingly utilities, of VGAM780 correlate with, and may be deduced from, the identity of the target genes which VGAM780 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30444] KIAA0471 (Accession NM\_014857) is a VGAM780 host target gene. KIAA0471 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0471, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0471 BINDING SITE, designated SEQ ID:16915, to the nucleotide sequence of VGAM780 RNA, herein designated VGAM RNA, also designated SEQ ID:3491.

[30445] A function of VGAM780 is therefore inhibition of KIAA0471 (Accession NM\_014857). Accordingly, utilities of VGAM780 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0471. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 781 (VGAM781) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30446] VGAM781 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM781 was detected is described hereinabove with reference to Figs. 1–8.

[30447] VGAM781 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Deer Tick Virus.

VGAM781 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30448] VGAM781 gene encodes a VGAM781 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM781 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM781 precursor RNA is designated SEQ ID:767, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:767 is located at position 6107 relative to the genome of Deer Tick Virus.

[30449] VGAM781 precursor RNA folds onto itself, forming

VGAM781 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30450] An enzyme complex designated DICER COMPLEX, `dices` the VGAM781 folded precursor RNA into VGAM781 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM781 RNA is designated SEQ ID:3492, and is provided hereinbelow with reference to the sequence listing part.

[30451] VGAM781 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM781 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM781 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30452] VGAM781 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM781 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM781 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM781 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM781 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30453] The complementary binding of VGAM781 RNA, herein designated VGAM RNA, to host target binding sites on VGAM781 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM781 host target RNA into VGAM781 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30454] It is appreciated that VGAM781 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM781 host target genes. The mRNA of each one of this plurality of VGAM781 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM781 RNA, herein designated VGAM RNA, and which when bound by VGAM781 RNA causes inhibition of translation of respective one or more VGAM781 host target proteins.

[30455] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM781 gene, herein designated VGAM GENE, on one or more VGAM781 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30456] It is yet further appreciated that a function of VGAM781 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM781 include diagnosis, prevention and treatment of viral infection by Deer Tick Virus. Specific functions, and accordingly utilities, of VGAM781 correlate with, and may be deduced from, the identity of the host target genes which VGAM781 binds and inhibits, and the

function of these host target genes, as elaborated herein–below.

[30457] Nucleotide sequences of the VGAM781 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM781 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM781 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM781 are further described hereinbelow with reference to Table 1.

[30458] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM781 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM781 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30459] As mentioned hereinabove with reference to Fig. 1, a function of VGAM781 gene, herein designated VGAM is inhibition of expression of VGAM781 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM781 correlate with, and may be deduced from, the identity of the target genes which VGAM781 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[30460] DKFZp762L0311 (Accession NM\_018719) is a VGAM781 host target gene. DKFZp762L0311 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp762L0311, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762L0311 BINDING SITE, designated SEQ ID:20798, to the nucleotide sequence of VGAM781 RNA, herein designated VGAM RNA, also designated SEQ ID:3492.

[30461] A function of VGAM781 is therefore inhibition of DKFZp762L0311 (Accession NM\_018719). Accordingly, utilities of VGAM781 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp762L0311. KIAA0182 (Accession XM\_050495) is another VGAM781 host target gene. KIAA0182 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0182, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0182 BINDING SITE, designated SEQ ID:35641, to the



nucleotide sequence of VGAM781 RNA, herein designated VGAM RNA, also designated SEQ ID:3492.

[30462] Another function of VGAM781 is therefore inhibition of KIAA0182 (Accession XM\_050495). Accordingly, utilities of VGAM781 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0182. KIAA1671 (Accession XM\_037809) is another VGAM781 host target gene. KIAA1671 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1671, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1671 BINDING SITE, designated SEQ ID:32690, to the nucleotide sequence of VGAM781 RNA, herein designated VGAM RNA, also designated SEQ ID:3492.

[30463] Another function of VGAM781 is therefore inhibition of KIAA1671 (Accession XM\_037809). Accordingly, utilities of VGAM781 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1671. LOC148823 (Accession NM\_145278) is another VGAM781 host target gene. LOC148823 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by LOC148823, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148823 BINDING SITE, designated SEQ ID:29790, to the nucleotide sequence of VGAM781 RNA, herein designated VGAM RNA, also designated SEQ ID:3492.

[30464] Another function of VGAM781 is therefore inhibition of LOC148823 (Accession NM\_145278). Accordingly, utilities of VGAM781 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148823. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 782 (VGAM782) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30465] VGAM782 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM782 was detected is described hereinabove with reference to Figs. 1–8.

[30466] VGAM782 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Deer Tick Virus.

VGAM782 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30467] VGAM782 gene encodes a VGAM782 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM782 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM782 precursor RNA is designated SEQ ID:768, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:768 is located at position 4906 relative to the genome of Deer Tick Virus.

[30468] VGAM782 precursor RNA folds onto itself, forming VGAM782 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30469] An enzyme complex designated DICER COMPLEX, `dices` the VGAM782 folded precursor RNA into VGAM782 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM782 RNA is designated SEQ ID:3493, and is provided hereinbelow with reference to the sequence listing part.

[30470] VGAM782 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM782 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM782 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30471] VGAM782 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM782 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM782 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM782 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM782 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30472] The complementary binding of VGAM782 RNA, herein designated VGAM RNA, to host target binding sites on VGAM782 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM782 host tar-

get RNA into VGAM782 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30473] It is appreciated that VGAM782 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM782 host target genes. The mRNA of each one of this plurality of VGAM782 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM782 RNA, herein designated VGAM RNA, and which when bound by VGAM782 RNA causes inhibition of translation of respective one or more VGAM782 host target proteins.

[30474] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM782 gene, herein designated VGAM GENE, on one or more VGAM782 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30475] It is yet further appreciated that a function of VGAM782 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of viral infection by Deer Tick Virus. Specific functions, and accordingly utilities, of VGAM782 correlate with, and may be deduced from, the identity of the host target genes which VGAM782 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30476] Nucleotide sequences of the VGAM782 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM782 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM782 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM782 are further

described hereinbelow with reference to Table 1.

[30477] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM782 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM782 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30478] As mentioned hereinabove with reference to Fig. 1, a function of VGAM782 gene, herein designated VGAM is inhibition of expression of VGAM782 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM782 correlate with, and may be deduced from, the identity of the target genes which VGAM782 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30479] Rho GDP Dissociation Inhibitor (GDI) Alpha (ARHGDIA, Accession NM\_004309) is a VGAM782 host target gene. ARHGDIA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGDIA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide



sequences of ARHGDIA BINDING SITE, designated SEQ ID:10515, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30480] A function of VGAM782 is therefore inhibition of Rho GDP Dissociation Inhibitor (GDI) Alpha (ARHGDIA, Accession NM\_004309), a gene which is a small guanine nucleotide exchange (GTP/GDP) factor. Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGDIA. The function of ARHGDIA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM435. Attractin (ATRN, Accession NM\_139321) is another VGAM782 host target gene. ATRN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATRN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATRN BINDING SITE, designated SEQ ID:29298, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30481] Another function of VGAM782 is therefore inhibition of Attractin (ATRN, Accession NM\_139321), a gene which is involved in the initial immune cell clustering during inflammatory response. Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATRN. The function of ATRN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM53. Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 3 (CBFA2T3, Accession NM\_005187) is another VGAM782 host target gene. CBFA2T3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CBFA2T3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CBFA2T3 BINDING SITE, designated SEQ ID:11688, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30482] Another function of VGAM782 is therefore inhibition of Core-binding Factor, Runt Domain, Alpha Subunit 2;

Translocated To, 3 (CBFA2T3, Accession NM\_005187). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBFA2T3. Centaurin, Delta 2 (CENTD2, Accession NM\_139181) is another VGAM782 host target gene. CENTD2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CENTD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CENTD2 BINDING SITE, designated SEQ ID:29196, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30483] Another function of VGAM782 is therefore inhibition of Centaurin, Delta 2 (CENTD2, Accession NM\_139181), a gene which involved in cell signaling/communication. Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CENTD2. The function of CENTD2 has been established by previous studies. Miura et al. (2002) examined ARAP1 as a possible link between phosphoinositide-, ARF-, and RHO-mediated cell signaling. In vitro, ARAP1

had RHO-GAP and phosphatidylinositol (3,4,5) trisphosphate (PIP3; OMIM Ref. No. 171834)-dependent ARF-GAP activity. ARAP1 associated with the Golgi. The RHO-GAP activity mediated cell rounding and loss of stress fibers when ARAP1 was overexpressed. The ARF-GAP activity mediated changes in the Golgi apparatus and the formation of filopodia, the latter a consequence of increased cellular activity of CDC42 (OMIM Ref. No. 116952). The ARF-GAP and RHO-GAP activities both contributed to inhibiting cell spreading. Thus, ARAP1 is a PIP3-dependent ARF-GAP that regulates ARF-, RHO-, and CDC42-dependent cell activities.

[30484] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30485] Miura, K.; Jacques, K. M.; Stauffer, S.; Kubosaki, A.; Zhu, K.; Hirsch, D. S.; Resau, J.; Zheng, Y.; Randazzo, P. A. : ARAP1: a point of convergence for Arf and Rho signaling. *Molec. Cell* 9: 109-119, 2002. ; and

[30486] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. XI. The.

[30487] Further studies establishing the function and utilities of CENTD2 are found in John Hopkins OMIM database record ID 606646, and in cited publications numbered 612 and 7048 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Discs, Large (Drosophila) Homolog 3 (neuroendocrine-dlg) (DLG3, Accession NM\_021120) is another VGAM782 host target gene. DLG3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DLG3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLG3 BINDING SITE, designated SEQ ID:22094, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30488] Another function of VGAM782 is therefore inhibition of Discs, Large (Drosophila) Homolog 3 (neuroendocrine-dlg) (DLG3, Accession NM\_021120), a gene which may interact with the cytoplasmic tail of the nmda receptor subunit nr2b . Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLG3. The function of DLG3 has been established by previous studies. Mutations of the

'discs large' (dlg) tumor suppressor locus in *Drosophila* lead to imaginal disc neoplasia and a prolonged larval period followed by death. *Drosophila* dlg and related proteins form a subfamily of the membrane-associated guanylate kinase (MAGUK) protein family and are important components of specialized cell junctions. See DLG1 (OMIM Ref. No. 601014). By searching an EST database for sequences related to dlg and DLG1, Makino et al. (1997) isolated a partial cDNA encoding NEDLG (neuroendocrine DLG). Using PCR, they cloned a cDNA corresponding to the entire NEDLG coding region. The predicted 817-amino acid protein contains the 3 DHR (discs large homologous region) segments, central SH3 motif, and C-terminal guanylate kinase domain characteristic of MAGUK proteins. NEDLG shares 75% and 60% protein sequence identity with DLG1 and *Drosophila* dlg, respectively. Northern blot analysis revealed that NEDLG is highly expressed in neuronal and endocrine tissues. Immunolocalization studies indicated that the protein was expressed mainly in nonproliferating cells, such as neurons, cells in Langerhans islets of the pancreas, myocytes of heart muscles, and the prickle and functional layer cells of the esophageal epithelium. In a yeast 2-hybrid assay, NEDLG

interacted with the C-terminal region of the APC (OMIM Ref. No. 175100) tumor suppressor protein. The authors suggested that NEDLG may negatively regulate cell proliferation through its interaction with the APC protein.

[30489] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30490] Makino, K.; Kuwahara, H.; Masuko, N.; Nishiyama, Y.; Morisaki, T.; Sasaki, J.; Nakao, M.; Kuwano, A.; Nakata, M.; Ushio, Y.; Saya, H. : Cloning and characterization of NE-dlg: a novel human homolog of the Drosophila discs large (dlg) tumor suppressor protein interacts with the APC protein. *Oncogene* 14: 2425–2433, 1997. ; and

[30491] Stathakis, D. G.; Lee, D.; Bryant, P. J. : DLG3, the gene encoding human neuroendocrine Dlg (NE-Dlg), is located within the 1.8-Mb dystonia-parkinsonism region at Xq13.1. *Genomics* 49: 3.

[30492] Further studies establishing the function and utilities of DLG3 are found in John Hopkins OMIM database record ID 300189, and in cited publications numbered 11386–11387 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Coagulation Factor VII (serum prothrombin conver-

sion accelerator) (F7, Accession NM\_019616) is another VGAM782 host target gene. F7 BINDING SITE1 and F7 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by F7, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F7 BINDING SITE1 and F7 BINDING SITE2, designated SEQ ID:21235 and SEQ ID:5606 respectively, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30493] Another function of VGAM782 is therefore inhibition of Coagulation Factor VII (serum prothrombin conversion accelerator) (F7, Accession NM\_019616). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F7. G Protein-coupled Receptor 56 (GPR56, Accession NM\_005682) is another VGAM782 host target gene. GPR56 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR56, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-



quences of GPR56 BINDING SITE, designated SEQ ID:12238, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30494] Another function of VGAM782 is therefore inhibition of G Protein-coupled Receptor 56 (GPR56, Accession NM\_005682), a gene which transduces extracellular signals through heterotrimeric G proteins. Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR56. The function of GPR56 has been established by previous studies. G protein-coupled receptors (GPRs), which are characterized by the presence of 7 transmembrane domains, are divided into several classes based on sequence characteristics. Class B GPRs, or the secretin-like receptors, include the secretin receptor (OMIM Ref. No. 182098) and the calcitonin receptor (OMIM Ref. No. 114131). The orphan receptors HE6 (OMIM Ref. No. 602657), CD97 (OMIM Ref. No. 601211), EMR1 (OMIM Ref. No. 600493), and BAI1 (OMIM Ref. No. 602682) share significant homology with class B GPRs across the 7-transmembrane region, but have a distinct N-terminal region containing a characteristic cysteine box, which

precedes the first membrane-spanning domain, and a mucin-like domain. By PCR of human cDNAs with degenerate primers based on conserved regions from secretin-like receptors, Liu et al. (1999) isolated a cDNA encoding a novel receptor, which they designated GPR56. The predicted 693-amino acid GPR56 protein shares 26 to 32% sequence identity with the 4 class B-like orphan receptors. Like these receptors, GPR56 contains 7 transmembrane domains as well as a mucin-like domain and cysteine box in the N-terminal region. Northern blot analysis revealed that the GPR56 gene was expressed as a 3-kb mRNA in a wide range of tissues, with the highest levels in thyroid. Using in situ hybridization, Liu et al. (1999) determined that the GPR56 gene was expressed selectively within the monolayer of cuboidal epithelial cells of the smaller, more actively secreting follicles of human thyroid. The GPR56 gene contains 13 exons and spans approximately 15 kb. Using differential display, Zendman et al. (1999) identified a GPR56 cDNA as a transcript that was differentially expressed in melanoma cell lines with different metastatic potential. They designated the gene TM7XN1 (7-transmembrane protein with no EGF-like N-terminal domains-1) because the protein lacks the EGF-

like domains found in the related GPRs CD97 and EMR1. Zendman et al. (1999) reported that the TM7XN1 protein contains 687 amino acids. RT-PCR and Northern blot analyses indicated that TM7XN1 gene expression was inversely correlated with metastatic potential in melanoma cell lines.

[30495] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30496] Liu, M.; Parker, R. M. C.; Darby, K.; Eyre, H. J.; Copeland, N. G.; Crawford, J.; Gilbert, D. J.; Sutherland, G. R.; Jenkins, N. A.; Herzog, H. : GPR56, a novel secretin-like human G-protein-coupled receptor gene. *Genomics* 55: 296-305, 1999. ; and

[30497] Zendman, A. J. W.; Cornelissen, I. M. H. A.; Weidle, U. H.; Ruiter, D. J.; van Muijen, G. N. P. : TM7XN1, a novel human EGF-TM7-like cDNA, detected with mRNA differential display using.

[30498] Further studies establishing the function and utilities of GPR56 are found in John Hopkins OMIM database record ID 604110, and in cited publications numbered 7062-7063 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer-

ence. Membrane Protein, Palmitoylated 2 (MAGUK p55 subfamily member 2) (MPP2, Accession XM\_008355) is another VGAM782 host target gene. MPP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MPP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MPP2 BINDING SITE, designated SEQ ID:30084, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30499] Another function of VGAM782 is therefore inhibition of Membrane Protein, Palmitoylated 2 (MAGUK p55 subfamily member 2) (MPP2, Accession XM\_008355). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MPP2. Male-specific Lethal 3-like 1 (Drosophila) (MSL3L1, Accession NM\_078630) is another VGAM782 host target gene. MSL3L1 BINDING SITE1 and MSL3L1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MSL3L1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus-

trates the complementarity of the nucleotide sequences of MSL3L1 BINDING SITE1 and MSL3L1 BINDING SITE2, designated SEQ ID:27814 and SEQ ID:27815 respectively, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30500] Another function of VGAM782 is therefore inhibition of Male-specific Lethal 3-like 1 (Drosophila) (MSL3L1, Accession NM\_078630). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSL3L1. ADAR3 (Accession NM\_018702) is another VGAM782 host target gene. ADAR3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ADAR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAR3 BINDING SITE, designated SEQ ID:20786, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30501] Another function of VGAM782 is therefore inhibition of ADAR3 (Accession NM\_018702). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with ADAR3. Chromosome 6 Open Reading Frame 9 (C6orf9, Accession NM\_022107) is another VGAM782 host target gene. C6orf9 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C6orf9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C6orf9 BINDING SITE, designated SEQ ID:22654, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30502] Another function of VGAM782 is therefore inhibition of Chromosome 6 Open Reading Frame 9 (C6orf9, Accession NM\_022107). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C6orf9. Cadherin-like 22 (CDH22, Accession NM\_021248) is another VGAM782 host target gene. CDH22 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CDH22, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the

nucleotide sequences of CDH22 BINDING SITE, designated SEQ ID:22214, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30503] Another function of VGAM782 is therefore inhibition of Cadherin-like 22 (CDH22, Accession NM\_021248). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH22. DKFZp547O146 (Accession NM\_020224) is another VGAM782 host target gene. DKFZp547O146 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547O146, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547O146 BINDING SITE, designated SEQ ID:21483, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30504] Another function of VGAM782 is therefore inhibition of DKFZp547O146 (Accession NM\_020224). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with DKFZp547O146. Fatty Acid Desaturase 2 (FADS2, Accession NM\_004265) is another VGAM782 host target gene. FADS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FADS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FADS2 BINDING SITE, designated SEQ ID:10466, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30505] Another function of VGAM782 is therefore inhibition of Fatty Acid Desaturase 2 (FADS2, Accession NM\_004265). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FADS2. FLJ11320 (Accession NM\_018389) is another VGAM782 host target gene. FLJ11320 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11320, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11320 BINDING SITE, designated SEQ ID:20427, to the



nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30506] Another function of VGAM782 is therefore inhibition of FLJ11320 (Accession NM\_018389). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11320. FLJ14351 (Accession NM\_024732) is another VGAM782 host target gene. FLJ14351 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ14351, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14351 BINDING SITE, designated SEQ ID:24071, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30507] Another function of VGAM782 is therefore inhibition of FLJ14351 (Accession NM\_024732). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14351. FLJ14816 (Accession NM\_032845) is another VGAM782 host target gene. FLJ14816 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ14816, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14816 BINDING SITE, designated SEQ ID:26637, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30508] Another function of VGAM782 is therefore inhibition of FLJ14816 (Accession NM\_032845). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14816. Gamma-glutamyltransferase-like Activity 4 (GGTLA4, Accession NM\_080920) is another VGAM782 host target gene. GGTLA4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GGTLA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GGTLA4 BINDING SITE, designated SEQ ID:28141, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30509] Another function of VGAM782 is therefore inhibition of

Gamma-glutamyltransferase-like Activity 4 (GGTLA4, Accession NM\_080920). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GGTLA4. KIAA0153 (Accession NM\_015140) is another VGAM782 host target gene. KIAA0153 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0153, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0153 BINDING SITE, designated SEQ ID:17497, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30510] Another function of VGAM782 is therefore inhibition of KIAA0153 (Accession NM\_015140). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0153. KIAA0285 (Accession NM\_014807) is another VGAM782 host target gene. KIAA0285 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0285, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0285 BINDING SITE, designated SEQ ID:16751, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30511] Another function of VGAM782 is therefore inhibition of KIAA0285 (Accession NM\_014807). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0285. KIAA0298 (Accession XM\_084529) is another VGAM782 host target gene. KIAA0298 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0298, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0298 BINDING SITE, designated SEQ ID:37625, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30512] Another function of VGAM782 is therefore inhibition of KIAA0298 (Accession XM\_084529). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0298. KIAA0376 (Accession XM\_037759) is another VGAM782 host target gene. KIAA0376 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0376, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0376 BINDING SITE, designated SEQ ID:32674, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30513] Another function of VGAM782 is therefore inhibition of KIAA0376 (Accession XM\_037759). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0376. KIAA0563 (Accession NM\_014834) is another VGAM782 host target gene. KIAA0563 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0563, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0563 BINDING SITE, designated SEQ ID:16842, to the nucleotide sequence of VGAM782 RNA, herein designated

VGAM RNA, also designated SEQ ID:3493.

[30514] Another function of VGAM782 is therefore inhibition of KIAA0563 (Accession NM\_014834). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0563. KIAA1076 (Accession XM\_037523) is another VGAM782 host target gene. KIAA1076 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1076, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1076 BINDING SITE, designated SEQ ID:32638, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30515] Another function of VGAM782 is therefore inhibition of KIAA1076 (Accession XM\_037523). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1076. KIAA1862 (Accession XM\_044212) is another VGAM782 host target gene. KIAA1862 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1862, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1862 BINDING SITE, designated SEQ ID:34174, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30516] Another function of VGAM782 is therefore inhibition of KIAA1862 (Accession XM\_044212). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1862. Myristoylated Alanine-rich Protein Kinase C Substrate (MARCKS, Accession NM\_002356) is another VGAM782 host target gene. MARCKS BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MARCKS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MARCKS BINDING SITE, designated SEQ ID:8167, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30517] Another function of VGAM782 is therefore inhibition of Myristoylated Alanine-rich Protein Kinase C Substrate

(MARCKS, Accession NM\_002356). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MARCKS. MGC4415 (Accession NM\_031484) is another VGAM782 host target gene. MGC4415 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4415, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4415 BINDING SITE, designated SEQ ID:25567, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30518] Another function of VGAM782 is therefore inhibition of MGC4415 (Accession NM\_031484). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4415. Serum Response Factor (c-fos serum response element-binding transcription factor) (SRF, Accession NM\_003131) is another VGAM782 host target gene. SRF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SRF, corresponding to a HOST TARGET binding site such as BINDING



SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRF BINDING SITE, designated SEQ ID:9098, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30519] Another function of VGAM782 is therefore inhibition of Serum Response Factor (c-fos serum response element-binding transcription factor) (SRF, Accession NM\_003131). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRF. STRAIT11499 (Accession NM\_021242) is another VGAM782 host target gene. STRAIT11499 BINDING SITE1 and STRAIT11499 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by STRAIT11499, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STRAIT11499 BINDING SITE1 and STRAIT11499 BINDING SITE2, designated SEQ ID:22209 and SEQ ID:22210 respectively, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30520] Another function of VGAM782 is therefore inhibition of STRAIT11499 (Accession NM\_021242). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STRAIT11499. LOC146562 (Accession NM\_139170) is another VGAM782 host target gene. LOC146562 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146562, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146562 BINDING SITE, designated SEQ ID:29179, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30521] Another function of VGAM782 is therefore inhibition of LOC146562 (Accession NM\_139170). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146562. LOC158856 (Accession XM\_098998) is another VGAM782 host target gene. LOC158856 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158856, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158856 BINDING SITE, designated SEQ ID:42033, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30522] Another function of VGAM782 is therefore inhibition of LOC158856 (Accession XM\_098998). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158856. LOC201220 (Accession XM\_113321) is another VGAM782 host target gene. LOC201220 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC201220, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201220 BINDING SITE, designated SEQ ID:42225, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30523] Another function of VGAM782 is therefore inhibition of LOC201220 (Accession XM\_113321). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC201220. LOC254057 (Accession XM\_173085) is another VGAM782 host target gene. LOC254057 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254057, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254057 BINDING SITE, designated SEQ ID:46342, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30524] Another function of VGAM782 is therefore inhibition of LOC254057 (Accession XM\_173085). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254057. LOC254205 (Accession XM\_172962) is another VGAM782 host target gene. LOC254205 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254205, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254205 BINDING SITE, designated SEQ ID:46217, to the nucleotide sequence of VGAM782 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3493.

[30525] Another function of VGAM782 is therefore inhibition of LOC254205 (Accession XM\_172962). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254205. LOC92340 (Accession XM\_044426) is another VGAM782 host target gene. LOC92340 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92340, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92340 BINDING SITE, designated SEQ ID:34199, to the nucleotide sequence of VGAM782 RNA, herein designated VGAM RNA, also designated SEQ ID:3493.

[30526] Another function of VGAM782 is therefore inhibition of LOC92340 (Accession XM\_044426). Accordingly, utilities of VGAM782 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92340. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 783 (VGAM783) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30527] VGAM783 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM783 was detected is described hereinabove with reference to Figs. 1–8.

[30528] VGAM783 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Deer Tick Virus. VGAM783 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30529] VGAM783 gene encodes a VGAM783 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM783 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM783 precursor RNA is designated SEQ ID:769, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:769 is located at position 1240 relative to the genome of Deer Tick Virus.

[30530] VGAM783 precursor RNA folds onto itself, forming

VGAM783 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30531] An enzyme complex designated DICER COMPLEX, `dices` the VGAM783 folded precursor RNA into VGAM783 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 49%) nucleotide sequence of VGAM783 RNA is designated SEQ ID:3494, and is provided hereinbelow with reference to the sequence listing part.

[30532] VGAM783 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM783 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM783 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30533] VGAM783 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM783 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM783 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM783 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM783 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example



only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30534] The complementary binding of VGAM783 RNA, herein designated VGAM RNA, to host target binding sites on VGAM783 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM783 host target RNA into VGAM783 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30535] It is appreciated that VGAM783 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM783 host target genes. The mRNA of each one of this plurality of VGAM783 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM783 RNA, herein designated VGAM RNA, and which when bound by VGAM783 RNA causes inhibition of translation of respective one or more VGAM783 host target proteins.

[30536] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM783 gene, herein designated VGAM GENE, on one or more VGAM783 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30537] It is yet further appreciated that a function of VGAM783 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of viral infection by Deer Tick Virus. Specific functions, and accordingly utilities, of VGAM783 correlate with, and may be deduced from, the identity of the host target genes which VGAM783 binds and inhibits, and the

function of these host target genes, as elaborated herein–below.

[30538] Nucleotide sequences of the VGAM783 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM783 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM783 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM783 are further described hereinbelow with reference to Table 1.

[30539] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM783 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM783 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30540] As mentioned hereinabove with reference to Fig. 1, a function of VGAM783 gene, herein designated VGAM is inhibition of expression of VGAM783 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM783 correlate with, and may be deduced from, the identity of the target genes which VGAM783 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[30541] MGC15429 (Accession NM\_032750) is a VGAM783 host target gene. MGC15429 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC15429, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15429 BINDING SITE, designated SEQ ID:26487, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30542] A function of VGAM783 is therefore inhibition of MGC15429 (Accession NM\_032750). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15429. Phospholipid Scramblase 4 (PLSCR4, Accession NM\_020353) is another VGAM783 host target gene. PLSCR4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLSCR4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLSCR4 BINDING SITE, designated SEQ

ID:21622, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30543] Another function of VGAM783 is therefore inhibition of Phospholipid Scramblase 4 (PLSCR4, Accession NM\_020353). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLSCR4. Regulator of G-protein Signalling 18 (RGS18, Accession NM\_130782) is another VGAM783 host target gene. RGS18 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RGS18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RGS18 BINDING SITE, designated SEQ ID:28270, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30544] Another function of VGAM783 is therefore inhibition of Regulator of G-protein Signalling 18 (RGS18, Accession NM\_130782). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RGS18. LOC122553

(Accession XM\_058630) is another VGAM783 host target gene. LOC122553 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC122553, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC122553 BINDING SITE, designated SEQ ID:36692, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30545] Another function of VGAM783 is therefore inhibition of LOC122553 (Accession XM\_058630). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC122553. LOC148195 (Accession XM\_097419) is another VGAM783 host target gene. LOC148195 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148195, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148195 BINDING SITE, designated SEQ ID:40880, to the nucleotide sequence of VGAM783 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3494.

[30546] Another function of VGAM783 is therefore inhibition of LOC148195 (Accession XM\_097419). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148195. LOC166341 (Accession XM\_093804) is another VGAM783 host target gene. LOC166341 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC166341, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC166341 BINDING SITE, designated SEQ ID:40213, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30547] Another function of VGAM783 is therefore inhibition of LOC166341 (Accession XM\_093804). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC166341. LOC254532 (Accession XM\_172961) is another VGAM783 host target gene. LOC254532 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254532, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254532 BINDING SITE, designated SEQ ID:46216, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30548] Another function of VGAM783 is therefore inhibition of LOC254532 (Accession XM\_172961). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254532. LOC257319 (Accession XM\_171049) is another VGAM783 host target gene. LOC257319 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257319, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257319 BINDING SITE, designated SEQ ID:45836, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30549] Another function of VGAM783 is therefore inhibition of LOC257319 (Accession XM\_171049). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with LOC257319. LOC51289 (Accession NM\_016568) is another VGAM783 host target gene. LOC51289 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51289, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51289 BINDING SITE, designated SEQ ID:18640, to the nucleotide sequence of VGAM783 RNA, herein designated VGAM RNA, also designated SEQ ID:3494.

[30550] Another function of VGAM783 is therefore inhibition of LOC51289 (Accession NM\_016568). Accordingly, utilities of VGAM783 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51289. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 784 (VGAM784) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30551] VGAM784 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM784 was detected is described hereinabove with reference to Figs. 1–8.

[30552] VGAM784 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Deer Tick Virus.

VGAM784 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30553] VGAM784 gene encodes a VGAM784 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM784 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM784 precursor RNA is designated SEQ ID:770, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:770 is located at position 834 relative to the genome of Deer Tick Virus.

[30554] VGAM784 precursor RNA folds onto itself, forming VGAM784 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30555] An enzyme complex designated DICER COMPLEX, `dices` the VGAM784 folded precursor RNA into VGAM784 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM784 RNA is designated SEQ ID:3495, and is provided hereinbelow with reference to the sequence listing part.

[30556] VGAM784 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM784 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM784 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30557] VGAM784 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM784 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM784 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM784 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM784 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30558] The complementary binding of VGAM784 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM784 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM784 host target RNA into VGAM784 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30559] It is appreciated that VGAM784 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM784 host target genes. The mRNA of each one of this plurality of VGAM784 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM784 RNA, herein designated VGAM RNA, and which when bound by VGAM784 RNA causes inhibition of translation of respective one or more VGAM784 host target proteins.

[30560] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM784 gene, herein designated VGAM GENE, on one or more VGAM784 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30561] It is yet further appreciated that a function of VGAM784 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM784 include diagnosis, prevention and treatment of viral infection by Deer Tick Virus. Specific functions, and accordingly utilities, of VGAM784 correlate with, and may be deduced from, the identity of the host target genes which VGAM784 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30562] Nucleotide sequences of the VGAM784 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM784 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM784 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM784 are further described hereinbelow with reference to Table 1.

[30563] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM784 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM784 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30564] As mentioned hereinabove with reference to Fig. 1, a function of VGAM784 gene, herein designated VGAM is inhibition of expression of VGAM784 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM784 correlate with, and may be deduced from, the identity of the target genes which VGAM784 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30565] Ras Homolog Gene Family, Member U (ARHU, Accession NM\_021205) is a VGAM784 host target gene. ARHU BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by ARHU, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHU BINDING SITE, designated SEQ ID:22181, to the nucleotide sequence of VGAM784 RNA, herein designated VGAM RNA, also designated SEQ ID:3495.

[30566] A function of VGAM784 is therefore inhibition of Ras Homolog Gene Family, Member U (ARHU, Accession NM\_021205). Accordingly, utilities of VGAM784 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHU. Chromosome 20 Open Reading Frame 42 (C20orf42, Accession NM\_017671) is another VGAM784 host target gene. C20orf42 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf42, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf42 BINDING SITE, designated SEQ ID:19213, to the nucleotide sequence of VGAM784 RNA, herein designated VGAM RNA, also designated SEQ ID:3495.



[30567] Another function of VGAM784 is therefore inhibition of Chromosome 20 Open Reading Frame 42 (C20orf42, Accession NM\_017671). Accordingly, utilities of VGAM784 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf42. DKFZp761D0614 (Accession XM\_113634) is another VGAM784 host target gene. DKFZp761D0614 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp761D0614, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761D0614 BINDING SITE, designated SEQ ID:42309, to the nucleotide sequence of VGAM784 RNA, herein designated VGAM RNA, also designated SEQ ID:3495.

[30568] Another function of VGAM784 is therefore inhibition of DKFZp761D0614 (Accession XM\_113634). Accordingly, utilities of VGAM784 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761D0614. KIAA1228 (Accession XM\_036408) is another VGAM784 host target gene. KIAA1228 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by KIAA1228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1228 BINDING SITE, designated SEQ ID:32442, to the nucleotide sequence of VGAM784 RNA, herein designated VGAM RNA, also designated SEQ ID:3495.

[30569] Another function of VGAM784 is therefore inhibition of KIAA1228 (Accession XM\_036408). Accordingly, utilities of VGAM784 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1228. LOC200473 (Accession XM\_117237) is another VGAM784 host target gene. LOC200473 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200473, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200473 BINDING SITE, designated SEQ ID:43312, to the nucleotide sequence of VGAM784 RNA, herein designated VGAM RNA, also designated SEQ ID:3495.

[30570] Another function of VGAM784 is therefore inhibition of LOC200473 (Accession XM\_117237). Accordingly, utilities

of VGAM784 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200473. LOC221296 (Accession XM\_166325) is another VGAM784 host target gene. LOC221296 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221296, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221296 BINDING SITE, designated SEQ ID:44170, to the nucleotide sequence of VGAM784 RNA, herein designated VGAM RNA, also designated SEQ ID:3495.

[30571] Another function of VGAM784 is therefore inhibition of LOC221296 (Accession XM\_166325). Accordingly, utilities of VGAM784 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221296. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 785 (VGAM785) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30572] VGAM785 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM785 was detected is described hereinabove with reference to Figs. 1–8.

[30573] VGAM785 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Zucchini Yellow Mosaic Virus. VGAM785 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30574] VGAM785 gene encodes a VGAM785 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM785 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM785 precursor RNA is designated SEQ ID:771, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:771 is located at position 7220 relative to the genome of Zucchini Yellow Mosaic Virus.

[30575] VGAM785 precursor RNA folds onto itself, forming VGAM785 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30576] An enzyme complex designated DICER COMPLEX, `dices` the VGAM785 folded precursor RNA into VGAM785 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM785 RNA is designated SEQ ID:3496, and is provided hereinbelow with reference to the sequence listing part.

[30577] VGAM785 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM785 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM785 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[30578] VGAM785 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM785 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM785 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM785 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM785 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30579] The complementary binding of VGAM785 RNA, herein designated VGAM RNA, to host target binding sites on VGAM785 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM785 host target RNA into VGAM785 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30580] It is appreciated that VGAM785 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM785 host target genes. The mRNA of each one of this plurality of VGAM785 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM785 RNA, herein designated VGAM RNA, and which when bound by VGAM785 RNA causes inhibition of translation of respective one or more VGAM785 host target proteins.

[30581] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM785 gene, herein designated VGAM GENE, on one or more VGAM785 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30582] It is yet further appreciated that a function of VGAM785 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM785 include diagnosis, prevention and treatment of viral infection by Zucchini Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM785 correlate with, and may be deduced from, the identity of the host target genes which VGAM785 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30583] Nucleotide sequences of the VGAM785 precursor RNA,



herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM785 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM785 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM785 are further  
described hereinbelow with reference to Table 1.

[30584] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM785 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM785 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[30585] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM785 gene, herein designated VGAM is  
inhibition of expression of VGAM785 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM785 correlate with, and may be deduced  
from, the identity of the target genes which VGAM785  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[30586] Calmodulin 3 (phosphorylase kinase, delta) (CALM3, Accession NM\_005184) is a VGAM785 host target gene. CALM3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CALM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CALM3 BINDING SITE, designated SEQ ID:11682, to the nucleotide sequence of VGAM785 RNA, herein designated VGAM RNA, also designated SEQ ID:3496.

[30587] A function of VGAM785 is therefore inhibition of Calmodulin 3 (phosphorylase kinase, delta) (CALM3, Accession NM\_005184), a gene which mediates the control of a large number of enzymes by  $Ca^{++}$ . Accordingly, utilities of VGAM785 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CALM3. The function of CALM3 has been established by previous studies. McPherson et al. (1991) assigned the CALM3 gene to chromosome 19 by study of somatic cell hybrids. By PCR-based amplification of CALM3-specific sequences using DNA from human/hamster cell hybrids as template, Berchtold et al. (1993) confirmed the assignment to chro-

mosome 19 and regionalized the gene to 19q13.2–q13.3 by in situ hybridization.

[30588] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30589] Berchtold, M. W.; Egli, R.; Rhyner, J. A.; Hameister, H.; Strehler, E. E. : Localization of the human bona fide calmodulin genes CALM1, CALM2, and CALM3 to chromosomes 14q24–q31, 2p21.1–p21.3, and 19q13.2–q13.3. Genomics 16: 461–465, 1993. ; and

[30590] McPherson, J. D.; Hickie, R. A.; Wasmuth, J. J.; Meyskens, F. L.; Perham, R. N.; Strehler, E. E.; Graham, M. T. : Chromosomal localization of multiple genes encoding calmodulin. (Abstra.

[30591] Further studies establishing the function and utilities of CALM3 are found in John Hopkins OMIM database record ID 114183, and in cited publications numbered 1257 and 12578 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LFG (Accession XM\_084780) is another VGAM785 host target gene. LFG BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LFG, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LFG BINDING SITE, designated SEQ ID:37691, to the nucleotide sequence of VGAM785 RNA, herein designated VGAM RNA, also designated SEQ ID:3496.

[30592] Another function of VGAM785 is therefore inhibition of LFG (Accession XM\_084780). Accordingly, utilities of VGAM785 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LFG. FLJ22029 (Accession NM\_024949) is another VGAM785 host target gene. FLJ22029 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22029, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22029 BINDING SITE, designated SEQ ID:24504, to the nucleotide sequence of VGAM785 RNA, herein designated VGAM RNA, also designated SEQ ID:3496.

[30593] Another function of VGAM785 is therefore inhibition of FLJ22029 (Accession NM\_024949). Accordingly, utilities of VGAM785 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22029.

SSH2 (Accession XM\_030846) is another VGAM785 host target gene. SSH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSH2 BINDING SITE, designated SEQ ID:31178, to the nucleotide sequence of VGAM785 RNA, herein designated VGAM RNA, also designated SEQ ID:3496.

[30594] Another function of VGAM785 is therefore inhibition of SSH2 (Accession XM\_030846). Accordingly, utilities of VGAM785 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSH2. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 786 (VGAM786) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30595] VGAM786 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM786 was detected is described

hereinabove with reference to Figs. 1–8.

[30596] VGAM786 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Zucchini Yellow Mosaic Virus. VGAM786 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30597] VGAM786 gene encodes a VGAM786 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM786 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM786 precursor RNA is designated SEQ ID:772, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:772 is located at position 8631 relative to the genome of Zucchini Yellow Mosaic Virus.

[30598] VGAM786 precursor RNA folds onto itself, forming VGAM786 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30599] An enzyme complex designated DICER COMPLEX, `dices` the VGAM786 folded precursor RNA into VGAM786 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM786 RNA is designated SEQ ID:3497, and is provided hereinbelow with reference to the sequence listing part.

[30600] VGAM786 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM786 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM786 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30601] VGAM786 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM786 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM786 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM786 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM786 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30602] The complementary binding of VGAM786 RNA, herein designated VGAM RNA, to host target binding sites on VGAM786 host target RNA, herein designated VGAM HOST



TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM786 host target RNA into VGAM786 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30603] It is appreciated that VGAM786 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM786 host target genes. The mRNA of each one of this plurality of VGAM786 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM786 RNA, herein designated VGAM RNA, and which when bound by VGAM786 RNA causes inhibition of translation of respective one or more VGAM786 host target proteins.

[30604] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM786 gene, herein designated VGAM GENE, on one or more VGAM786 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30605] It is yet further appreciated that a function of VGAM786 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of viral infection by Zucchini Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM786 correlate with, and may be deduced from, the identity of the host target genes which VGAM786 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30606] Nucleotide sequences of the VGAM786 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM786 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM786 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM786 are further described hereinbelow with reference to Table 1.

[30607] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM786 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM786 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30608] As mentioned hereinabove with reference to Fig. 1, a function of VGAM786 gene, herein designated VGAM is inhibition of expression of VGAM786 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM786 correlate with, and may be deduced from, the identity of the target genes which VGAM786 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30609] Aristaless-like Homeobox 3 (ALX3, Accession NM\_006492) is a VGAM786 host target gene. ALX3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALX3, corresponding to a HOST TARGET binding site such as BINDING SITE

I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALX3 BINDING SITE, designated SEQ ID:13220, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30610] A function of VGAM786 is therefore inhibition of Arista-less-like Homeobox 3 (ALX3, Accession NM\_006492), a gene which is involved in cell-type differentiation and development. Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALX3. The function of ALX3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM55. Asparagine Synthetase (ASNS, Accession NM\_133436) is another VGAM786 host target gene. ASNS BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ASNS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASNS BINDING SITE, designated SEQ ID:28515, to the nucleotide sequence of VGAM786 RNA, herein designated

VGAM RNA, also designated SEQ ID:3497.

[30611] Another function of VGAM786 is therefore inhibition of Asparagine Synthetase (ASNS, Accession NM\_133436). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASNS. Erythrocyte Membrane Protein Band 4.9 (dematin) (EPB49, Accession NM\_001978) is another VGAM786 host target gene. EPB49 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPB49, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPB49 BINDING SITE, designated SEQ ID:7708, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30612] Another function of VGAM786 is therefore inhibition of Erythrocyte Membrane Protein Band 4.9 (dematin) (EPB49, Accession NM\_001978), a gene which is an actin-bundling protein. Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPB49. The function of EPB49 and its association with various diseases and clinical con-

ditions, has been established by previous studies, as described hereinabove with reference to

VGAM760.Fibroblast Growth Factor Receptor 2

(bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome) (FGFR2, Accession NM\_000141) is another VGAM786 host target gene. FGFR2 BINDING SITE1 through FGFR2 BINDING SITE6 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGFR2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGFR2 BINDING SITE1 through FGFR2 BINDING SITE6, designated SEQ ID:5638, SEQ ID:23300, SEQ ID:23234, SEQ ID:23241, SEQ ID:23288 and SEQ ID:23294 respectively, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30613] Another function of VGAM786 is therefore inhibition of Fibroblast Growth Factor Receptor 2 (bacteria-expressed kinase, keratinocyte growth factor receptor, craniofacial dysostosis 1, Crouzon syndrome, Pfeiffer syndrome, Jackson-Weiss syndrome) (FGFR2, Accession NM\_000141).

Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGFR2. Glutamate Receptor, Metabotropic 1 (GRM1, Accession NM\_000838) is another VGAM786 host target gene. GRM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRM1 BINDING SITE, designated SEQ ID:6496, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30614] Another function of VGAM786 is therefore inhibition of Glutamate Receptor, Metabotropic 1 (GRM1, Accession NM\_000838), a gene which promotes phosphoinositide hydrolysis. Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRM1. The function of GRM1 has been established by previous studies. Stephan et al. (1996) isolated 2 splice variants of mGluR1 from a human cerebellum cDNA library. The 3.3- and 5.6-kb clones encoded mGluR1-beta and mGluR1-alpha, respectively.

Northern blot analysis showed that mGluR1 mRNA was expressed in the highest levels in the cerebellum, followed by cerebral cortex, thalamus, subthalamic nucleus, and amygdala. Lower levels were also detected in the hippocampus, substantia nigra, caudate nucleus, and putamen. Little or no mRNA was detected in spinal cord or corpus callosum. Animal model experiments lend further support to the function of GRM1. Aiba et al. (1994) generated a mouse strain deficient in GluR1 by targeted disruption. Gross anatomy of the hippocampus, excitatory synaptic transmission, long-term depression, and short-term potentiation in the hippocampal CA1 region were all apparently normal in the mutant mice. In contrast, long-term potentiation was substantially reduced, and a moderate level of impairment was observed in context-specific associative learning. Aiba et al. (1994) proposed that GluR1 is not 'in line' in long-term potentiation production, but rather modulates the plasticity process, and hence affects context-specific associative learning. Aiba et al. (1994) found that the GluR1 mutant mice were viable but showed characteristic cerebellar symptoms, such as ataxic gait and intention tremor. The anatomy of the cerebellum was not overtly disturbed. Excitatory synaptic transmis-



sion from parallel fibers to Purkinje cells and that from climbing fibers to Purkinje cells appeared to be functional, and voltage-gated calcium channels of Purkinje cells were normal. Both parallel fibers and climbing fiber synapses displayed normal short-term synaptic plasticity to paired stimuli. By marked contrast, long-term depression was clearly deficient and conditioned eyeblink response was impaired. Aiba et al. (1994) concluded that GluR1 was required for the induction of long-term depression.

[30615] It is appreciated that the abovementioned animal model for GRM1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[30616] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30617] Aiba, A.; Chen, C.; Herrup, K.; Rosenmund, C.; Stevens, C. F.; Tonegawa, S. : Reduced hippocampal long-term potentiation and context-specific deficit in associative learning in mGluR1 mutant mice. Cell 79: 365-375, 1994. ; and

[30618] Stephan, D.; Bon, C.; Holzwarth, J. A.; Galvan, M.; Pruss, R. M. : Human metabotropic glutamate receptor 1: mRNA

distribution, chromosome localization and functional expression of two.

[30619] Further studies establishing the function and utilities of GRM1 are found in John Hopkins OMIM database record ID 604473, and in cited publications numbered 4924–4925, 7056–493 and 4920 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Kallmann Syndrome 1 Sequence (KAL1, Accession NM\_000216) is another VGAM786 host target gene. KAL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KAL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KAL1 BINDING SITE, designated SEQ ID:5717, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30620] Another function of VGAM786 is therefore inhibition of Kallmann Syndrome 1 Sequence (KAL1, Accession NM\_000216). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KAL1. Antigen Identified By Monoclonal Antibody Ki-67 (MKI67, Accession

NM\_002417) is another VGAM786 host target gene.

MKI67 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MKI67, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MKI67 BINDING SITE, designated SEQ ID:8254, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30621] Another function of VGAM786 is therefore inhibition of Antigen Identified By Monoclonal Antibody Ki-67 (MKI67, Accession NM\_002417), a gene which thought to be required for maintaining cell proliferation. Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MKI67. The function of MKI67 has been established by previous studies. Ki-67 is a commercially available monoclonal antibody that reacts with a nuclear antigen expressed in proliferating cells but not in quiescent cells. Expression of this antigen occurs preferentially during late G1, S, G2, and M phases of the cell cycle, while in cells in G0 phase the antigen cannot be detected. Consequently, the antibody is used in tumor pathology to detect proliferating cells.

erating cells in neoplastic diseases. In cultured cells an antigen in the nucleolus of interphase cells stains with Ki-67, which, furthermore, reacts with an interchromatinous network during mitosis. From study of a panel of human-rodent somatic cell hybrids, Schonk et al. (1989) demonstrated that a gene involved in the expression of the antigen is located on chromosome 10. By in situ hybridization, Fonatsch et al. (1991) regionalized the MKI67 gene to 10q25-qter. By FISH, Traut et al. (1998) mapped the mouse Mki67 gene to chromosome 7F3-F5. By immunoscreening a cDNA expression library, followed by RT-PCR and 5-prime and 3-prime RACE, Schluter et al. (1993) isolated 2 cDNAs encoding isoforms of Ki-67. Genomic sequence analysis determined that the Ki-67 gene contains 15 exons. The Ki-67 repeat region, within which there is a 22-amino acid Ki-67 motif, is encoded by exon 13. The shorter isoform lacks exon 7. Northern blot analysis revealed multiple transcripts ranging from approximately 8.9 to 12.5 kb in proliferating but not quiescent cells. Immunoblot analysis showed expression of 320- and 359-kD proteins. Sequence analysis predicted that the short-lived 2,896- and 3,256-amino acid protein isoforms contain potential nuclear targeting signals, over

200 potential phosphorylation sites, 19 N-myristoylation sites, 3 amidation sites, and numerous PEST sites. Anti-sense oligonucleotides inhibited cellular proliferation in a dose-dependent manner, suggesting that Ki-67 protein expression may be an absolute requirement for cell proliferation.

[30622] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30623] Schluter, C.; Duchrow, M.; Wohlenberg, C.; Becker, M. H. G.; Key, G.; Flad, H.-D.; Gerdes, J. : The cell proliferation-associated antigen of antibody Ki-67: a very large, ubiquitous nuclear protein with numerous repeated elements, representing a new kind of cell cycle-maintaining proteins. J. Cell. Biol. 123: 513-522, 1993. ; and

[30624] Traut, W.; Scholzen, T.; Winking, H.; Kubbutat, M. H. G.; Gerdes, J. : Assignment of the murine Ki-67 gene (Mki67) to chromosome band 7F3-F5 by in situ hybridization. Cytogenet. Cell Ge.

[30625] Further studies establishing the function and utilities of MKI67 are found in John Hopkins OMIM database record ID 176741, and in cited publications numbered 1794-1797 listed in the bibliography section hereinbelow,

which are also hereby incorporated by reference. Serine (or cysteine) Proteinase Inhibitor, Clade H (heat shock protein 47), Member 2 (SERPINH2, Accession NM\_001235) is another VGAM786 host target gene. SERPINH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SERPINH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SERPINH2 BINDING SITE, designated SEQ ID:6905, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30626] Another function of VGAM786 is therefore inhibition of Serine (or cysteine) Proteinase Inhibitor, Clade H (heat shock protein 47), Member 2 (SERPINH2, Accession NM\_001235), a gene which binds to collagen. could be involved as a chaperone in the biosynthetic pathway of collagen. Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SERPINH2. The function of SERPINH2 has been established by previous studies. Collagen-binding proteins, or colligins, are glycoproteins localized to endoplasmic reticulum that belong to the serpin

(serine protease inhibitor) family. Ikegawa et al. (1995) isolated and characterized a full-length human cDNA clone that encodes a 418-amino acid peptide highly homologous (97% identity) to the human colligin-1 gene (OMIM Ref. No. 600942) previously reported by Clarke and Sanwal (1992). Ikegawa et al. (1995) called the novel gene colligin-2 and identified a genomic clone that contained the entire coding sequence of the cDNA. By fluorescence in situ hybridization they determined its chromosomal localization on 11q13.5. The authors found that the colligin-2 gene is expressed ubiquitously among all normal human tissues except brain and circulating leukocytes. Ikegawa and Nakamura (1997) found that the CBP2 gene spans approximately 11 kb of genomic DNA and consists of 5 exons. The promoter sequence of the human gene shows significant homology to that of its murine counterpart, which contains several regulatory sequences including heat-shock and retinoic acid-responsive elements. The findings suggested that colligin may function as a collagen-specific molecular chaperone and play a role in the process of retinoic acid-induced differentiation.

[30627] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

[30628] Ikegawa, S.; Sudo, K.; Okui, K.; Nakamura, Y. : Isolation, characterization and chromosomal assignment of human colligin-2 gene (CBP2). Cytogenet. Cell Genet. 71: 182-186, 1995. ; and

[30629] Ikegawa, S.; Sudo, K.; Okui, K.; Nakamura, Y. : Isolation, characterization and chromosomal assignment of human colligin-2 gene (CBP2). Cytogenet. Cell Genet. 71: 182-186, 1995.

[30630] Further studies establishing the function and utilities of SERPINH2 are found in John Hopkins OMIM database record ID 600943, and in cited publications numbered 1288-1290 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZP434O125 (Accession XM\_036284) is another VGAM786 host target gene. DKFZP434O125 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434O125, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434O125 BINDING SITE, designated SEQ ID:32404, to the nucleotide sequence of VGAM786 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3497.

[30631] Another function of VGAM786 is therefore inhibition of DKFZP434O125 (Accession XM\_036284). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434O125. Dystrophia Myotonica-containing WD Repeat Motif (DMWD, Accession XM\_027569) is another VGAM786 host target gene. DMWD BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DMWD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DMWD BINDING SITE, designated SEQ ID:30527, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30632] Another function of VGAM786 is therefore inhibition of Dystrophia Myotonica-containing WD Repeat Motif (DMWD, Accession XM\_027569). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DMWD. FLJ14106 (Accession NM\_025067) is another VGAM786 host target gene. FLJ14106 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ14106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14106 BINDING SITE, designated SEQ ID:24664, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30633] Another function of VGAM786 is therefore inhibition of FLJ14106 (Accession NM\_025067). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14106. FLJ20202 (Accession NM\_017709) is another VGAM786 host target gene. FLJ20202 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20202, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20202 BINDING SITE, designated SEQ ID:19288, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30634] Another function of VGAM786 is therefore inhibition of

FLJ20202 (Accession NM\_017709). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20202. FLJ20255 (Accession NM\_017728) is another VGAM786 host target gene. FLJ20255 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20255 BINDING SITE, designated SEQ ID:19317, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30635] Another function of VGAM786 is therefore inhibition of FLJ20255 (Accession NM\_017728). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20255. KIAA0426 (Accession NM\_014724) is another VGAM786 host target gene. KIAA0426 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0426, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0426 BINDING SITE, designated SEQ ID:16311, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30636] Another function of VGAM786 is therefore inhibition of KIAA0426 (Accession NM\_014724). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0426. LEC3 (Accession NM\_015236) is another VGAM786 host target gene. LEC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LEC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LEC3 BINDING SITE, designated SEQ ID:17568, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30637] Another function of VGAM786 is therefore inhibition of LEC3 (Accession NM\_015236). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LEC3. MGC16384 (Accession NM\_053048) is another VGAM786

host target gene. MGC16384 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC16384, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC16384 BINDING SITE, designated SEQ ID:27594, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30638] Another function of VGAM786 is therefore inhibition of MGC16384 (Accession NM\_053048). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC16384. NDP52 (Accession NM\_005831) is another VGAM786 host target gene. NDP52 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NDP52, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDP52 BINDING SITE, designated SEQ ID:12441, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30639] Another function of VGAM786 is therefore inhibition of NDP52 (Accession NM\_005831). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDP52. SCMH1 (Accession NM\_012236) is another VGAM786 host target gene. SCMH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCMH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCMH1 BINDING SITE, designated SEQ ID:14538, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30640] Another function of VGAM786 is therefore inhibition of SCMH1 (Accession NM\_012236). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCMH1. Serine (or cysteine) Proteinase Inhibitor, Clade H (heat shock protein 47), Member 1, (collagen binding protein 1) (SERPINH1, Accession NM\_004353) is another VGAM786 host target gene. SERPINH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by SERPINH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SERPINH1 BINDING SITE, designated SEQ ID:10559, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30641] Another function of VGAM786 is therefore inhibition of Serine (or cysteine) Proteinase Inhibitor, Clade H (heat shock protein 47), Member 1, (collagen binding protein 1) (SERPINH1, Accession NM\_004353). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SERPINH1. Zinc Finger Protein 317 (ZNF317, Accession XM\_050435) is another VGAM786 host target gene. ZNF317 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF317 BINDING SITE, designated SEQ ID:35637, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ

ID:3497.

[30642] Another function of VGAM786 is therefore inhibition of Zinc Finger Protein 317 (ZNF317, Accession XM\_050435). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF317. LOC201229 (Accession XM\_113925) is another VGAM786 host target gene. LOC201229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201229 BINDING SITE, designated SEQ ID:42538, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30643] Another function of VGAM786 is therefore inhibition of LOC201229 (Accession XM\_113925). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201229. LOC201799 (Accession XM\_114380) is another VGAM786 host target gene. LOC201799 BINDING SITE is HOST TARGET binding site found in the 3' un-



translated region of mRNA encoded by LOC201799, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201799 BINDING SITE, designated SEQ ID:42915, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30644] Another function of VGAM786 is therefore inhibition of LOC201799 (Accession XM\_114380). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201799. LOC221272 (Accession XM\_168050) is another VGAM786 host target gene. LOC221272 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221272, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221272 BINDING SITE, designated SEQ ID:44962, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30645] Another function of VGAM786 is therefore inhibition of LOC221272 (Accession XM\_168050). Accordingly, utilities

of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221272. LOC91056 (Accession XM\_170662) is another VGAM786 host target gene. LOC91056 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91056 BINDING SITE, designated SEQ ID:45439, to the nucleotide sequence of VGAM786 RNA, herein designated VGAM RNA, also designated SEQ ID:3497.

[30646] Another function of VGAM786 is therefore inhibition of LOC91056 (Accession XM\_170662). Accordingly, utilities of VGAM786 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91056. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 787 (VGAM787) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30647] VGAM787 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM787 was detected is described hereinabove with reference to Figs. 1–8.

[30648] VGAM787 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Zucchini Yellow Mosaic Virus. VGAM787 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30649] VGAM787 gene encodes a VGAM787 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM787 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM787 precursor RNA is designated SEQ ID:773, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:773 is located at position 3152 relative to the genome of Zucchini Yellow Mosaic Virus.

[30650] VGAM787 precursor RNA folds onto itself, forming VGAM787 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30651] An enzyme complex designated DICER COMPLEX, `dices` the VGAM787 folded precursor RNA into VGAM787 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM787 RNA is designated SEQ ID:3498, and is provided hereinbelow with reference to the sequence listing part.

[30652] VGAM787 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM787 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM787 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[30653] VGAM787 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM787 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM787 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM787 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM787 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30654] The complementary binding of VGAM787 RNA, herein designated VGAM RNA, to host target binding sites on VGAM787 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM787 host target RNA into VGAM787 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30655] It is appreciated that VGAM787 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM787 host target genes. The mRNA of each one of this plurality of VGAM787 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM787 RNA, herein designated VGAM RNA, and which when bound by VGAM787 RNA causes inhibition of translation of respective one or more VGAM787 host target proteins.

[30656] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM787 gene, herein designated VGAM GENE, on one or more VGAM787 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30657] It is yet further appreciated that a function of VGAM787 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of viral infection by Zucchini Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM787 correlate with, and may be deduced from, the identity of the host target genes which VGAM787 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30658] Nucleotide sequences of the VGAM787 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM787 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM787 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM787 are further  
described hereinbelow with reference to Table 1.

[30659] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM787 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM787 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[30660] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM787 gene, herein designated VGAM is  
inhibition of expression of VGAM787 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM787 correlate with, and may be deduced  
from, the identity of the target genes which VGAM787  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[30661] Chloride Channel 4 (CLCN4, Accession NM\_001830) is a  
VGAM787 host target gene. CLCN4 BINDING SITE is HOST



TARGET binding site found in the 3` untranslated region of mRNA encoded by CLCN4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLCN4 BINDING SITE, designated SEQ ID:7571, to the nucleotide sequence of VGAM787 RNA, herein designated VGAM RNA, also designated SEQ ID:3498.

[30662] A function of VGAM787 is therefore inhibition of Chloride Channel 4 (CLCN4, Accession NM\_001830), a gene which is regulation of cell volume; membrane potential stabilization, signal transduction and transepithelial transport. Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCN4. The function of CLCN4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM558. Chromosome X Open Reading Frame 1 (CXorf1, Accession NM\_004709) is another VGAM787 host target gene. CXorf1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CXorf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CXorf1 BINDING SITE, designated SEQ ID:11055, to the nucleotide sequence of VGAM787 RNA, herein designated VGAM RNA, also designated SEQ ID:3498.

[30663] Another function of VGAM787 is therefore inhibition of Chromosome X Open Reading Frame 1 (CXorf1, Accession NM\_004709). Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CXorf1. General Transcription Factor IIE, Polypeptide 1, Alpha 56kDa (GTF2E1, Accession NM\_005513) is another VGAM787 host target gene. GTF2E1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GTF2E1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GTF2E1 BINDING SITE, designated SEQ ID:12038, to the nucleotide sequence of VGAM787 RNA, herein designated VGAM RNA, also designated SEQ ID:3498.

[30664] Another function of VGAM787 is therefore inhibition of General Transcription Factor IIE, Polypeptide 1, Alpha

56kDa (GTF2E1, Accession NM\_005513). Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GTF2E1. MADP-1 (Accession NM\_033114) is another VGAM787 host target gene. MADP-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MADP-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MADP-1 BINDING SITE, designated SEQ ID:26962, to the nucleotide sequence of VGAM787 RNA, herein designated VGAM RNA, also designated SEQ ID:3498.

[30665] Another function of VGAM787 is therefore inhibition of MADP-1 (Accession NM\_033114). Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MADP-1. LOC120856 (Accession XM\_058509) is another VGAM787 host target gene. LOC120856 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120856, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of LOC120856 BINDING SITE, designated SEQ ID:36637, to the nucleotide sequence of VGAM787 RNA, herein designated VGAM RNA, also designated SEQ ID:3498.

[30666] Another function of VGAM787 is therefore inhibition of LOC120856 (Accession XM\_058509). Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120856. LOC152756 (Accession XM\_098262) is another VGAM787 host target gene. LOC152756 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152756, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152756 BINDING SITE, designated SEQ ID:41548, to the nucleotide sequence of VGAM787 RNA, herein designated VGAM RNA, also designated SEQ ID:3498.

[30667] Another function of VGAM787 is therefore inhibition of LOC152756 (Accession XM\_098262). Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152756. LOC157931 (Accession XM\_098845) is an-

other VGAM787 host target gene. LOC157931 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157931, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157931 BINDING SITE, designated SEQ ID:41904, to the nucleotide sequence of VGAM787 RNA, herein designated VGAM RNA, also designated SEQ ID:3498.

[30668] Another function of VGAM787 is therefore inhibition of LOC157931 (Accession XM\_098845). Accordingly, utilities of VGAM787 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157931. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 788 (VGAM788) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30669] VGAM788 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM788 was detected is described

hereinabove with reference to Figs. 1–8.

[30670] VGAM788 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Zucchini Yellow Mosaic Virus. VGAM788 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30671] VGAM788 gene encodes a VGAM788 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM788 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM788 precursor RNA is designated SEQ ID:774, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:774 is located at position 2523 relative to the genome of Zucchini Yellow Mosaic Virus.

[30672] VGAM788 precursor RNA folds onto itself, forming VGAM788 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30673] An enzyme complex designated DICER COMPLEX, `dices` the VGAM788 folded precursor RNA into VGAM788 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM788 RNA is designated SEQ ID:3499, and is provided hereinbelow with reference to the sequence listing part.

[30674] VGAM788 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM788 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM788 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30675] VGAM788 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM788 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM788 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM788 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM788 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30676] The complementary binding of VGAM788 RNA, herein designated VGAM RNA, to host target binding sites on VGAM788 host target RNA, herein designated VGAM HOST



TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM788 host target RNA into VGAM788 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30677] It is appreciated that VGAM788 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM788 host target genes. The mRNA of each one of this plurality of VGAM788 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM788 RNA, herein designated VGAM RNA, and which when bound by VGAM788 RNA causes inhibition of translation of respective one or more VGAM788 host target proteins.

[30678] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM788 gene, herein designated VGAM GENE, on one or more VGAM788 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30679] It is yet further appreciated that a function of VGAM788 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM788 include diagnosis, prevention and treatment of viral infection by Zucchini Yellow Mosaic Virus. Specific functions, and accordingly utilities, of VGAM788 correlate with, and may be deduced from, the identity of the host target genes which VGAM788 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30680] Nucleotide sequences of the VGAM788 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM788 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM788 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM788 are further described hereinbelow with reference to Table 1.

[30681] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM788 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM788 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30682] As mentioned hereinabove with reference to Fig. 1, a function of VGAM788 gene, herein designated VGAM is inhibition of expression of VGAM788 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM788 correlate with, and may be deduced from, the identity of the target genes which VGAM788 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30683] FLJ10178 (Accession NM\_018015) is a VGAM788 host target gene. FLJ10178 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10178, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10178 BINDING SITE, designated SEQ ID:19753, to the nucleotide sequence of VGAM788 RNA, herein designated VGAM RNA, also designated SEQ ID:3499.

[30684] A function of VGAM788 is therefore inhibition of FLJ10178 (Accession NM\_018015). Accordingly, utilities of VGAM788 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10178. FLJ12681 (Accession NM\_022773) is another VGAM788 host target gene. FLJ12681 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12681, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12681 BINDING SITE, designated SEQ ID:23036, to the nucleotide sequence of VGAM788 RNA, herein designated VGAM RNA, also designated SEQ ID:3499.

[30685] Another function of VGAM788 is therefore inhibition of FLJ12681 (Accession NM\_022773). Accordingly, utilities of VGAM788 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12681.

FLJ32865 (Accession NM\_144613) is another VGAM788 host target gene. FLJ32865 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ32865, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32865 BINDING SITE, designated SEQ ID:29430, to the nucleotide sequence of VGAM788 RNA, herein designated VGAM RNA, also designated SEQ ID:3499.

[30686] Another function of VGAM788 is therefore inhibition of FLJ32865 (Accession NM\_144613). Accordingly, utilities of VGAM788 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32865. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 789 (VGAM789) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30687] VGAM789 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM789 was detected is described

hereinabove with reference to Figs. 1–8.

[30688] VGAM789 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM789 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30689] VGAM789 gene encodes a VGAM789 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM789 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM789 precursor RNA is designated SEQ ID:775, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:775 is located at position 4478 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30690] VGAM789 precursor RNA folds onto itself, forming VGAM789 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[30691] An enzyme complex designated DICER COMPLEX, `dices` the VGAM789 folded precursor RNA into VGAM789 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM789 RNA is designated SEQ ID:3500, and is provided hereinbelow with reference to the sequence listing part.

[30692] VGAM789 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM789 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM789 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30693] VGAM789 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM789 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM789 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM789 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM789 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30694] The complementary binding of VGAM789 RNA, herein designated VGAM RNA, to host target binding sites on VGAM789 host target RNA, herein designated VGAM HOST



TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM789 host target RNA into VGAM789 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30695] It is appreciated that VGAM789 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM789 host target genes. The mRNA of each one of this plurality of VGAM789 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM789 RNA, herein designated VGAM RNA, and which when bound by VGAM789 RNA causes inhibition of translation of respective one or more VGAM789 host target proteins.

[30696] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM789 gene, herein designated VGAM GENE, on one or more VGAM789 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30697] It is yet further appreciated that a function of VGAM789 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM789 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM789 correlate with, and may be deduced from, the identity of the host target genes which VGAM789 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30698] Nucleotide sequences of the VGAM789 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM789 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM789 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM789 are further described hereinbelow with reference to Table 1.

[30699] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM789 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM789 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30700] As mentioned hereinabove with reference to Fig. 1, a function of VGAM789 gene, herein designated VGAM is inhibition of expression of VGAM789 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM789 correlate with, and may be deduced from, the identity of the target genes which VGAM789 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30701] Vesicle Amine Transport Protein 1 Homolog (T californica) (VAT1, Accession NM\_006373) is a VGAM789 host target gene. VAT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

VAT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VAT1 BINDING SITE, designated SEQ ID:13066, to the nucleotide sequence of VGAM789 RNA, herein designated VGAM RNA, also designated SEQ ID:3500.

[30702] A function of VGAM789 is therefore inhibition of Vesicle Amine Transport Protein 1 Homolog (T californica) (VAT1, Accession NM\_006373), a gene which is a membrane protein of cholinergic synaptic vesicles. Accordingly, utilities of VGAM789 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VAT1. The function of VAT1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM212. Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698) is another VGAM789 host target gene. BLCAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BLCAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLCAP BINDING SITE, designated SEQ

ID:13523, to the nucleotide sequence of VGAM789 RNA, herein designated VGAM RNA, also designated SEQ ID:3500.

[30703] Another function of VGAM789 is therefore inhibition of Bladder Cancer Associated Protein (BLCAP, Accession NM\_006698). Accordingly, utilities of VGAM789 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLCAP. LOC152790 (Accession XM\_098264) is another VGAM789 host target gene. LOC152790 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152790, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152790 BINDING SITE, designated SEQ ID:41554, to the nucleotide sequence of VGAM789 RNA, herein designated VGAM RNA, also designated SEQ ID:3500.

[30704] Another function of VGAM789 is therefore inhibition of LOC152790 (Accession XM\_098264). Accordingly, utilities of VGAM789 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152790. LOC162333 (Accession XM\_102591) is an-

other VGAM789 host target gene. LOC162333 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC162333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162333 BINDING SITE, designated SEQ ID:42121, to the nucleotide sequence of VGAM789 RNA, herein designated VGAM RNA, also designated SEQ ID:3500.

[30705] Another function of VGAM789 is therefore inhibition of LOC162333 (Accession XM\_102591). Accordingly, utilities of VGAM789 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162333. LOC202126 (Accession XM\_117362) is another VGAM789 host target gene. LOC202126 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202126, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202126 BINDING SITE, designated SEQ ID:43412, to the nucleotide sequence of VGAM789 RNA, herein designated VGAM RNA, also designated SEQ ID:3500.

[30706] Another function of VGAM789 is therefore inhibition of LOC202126 (Accession XM\_117362). Accordingly, utilities of VGAM789 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202126. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 790 (VGAM790) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30707] VGAM790 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM790 was detected is described hereinabove with reference to Figs. 1–8.

[30708] VGAM790 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM790 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30709] VGAM790 gene encodes a VGAM790 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM790

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM790 precursor RNA is designated SEQ ID:776, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:776 is located at position 5279 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30710] VGAM790 precursor RNA folds onto itself, forming VGAM790 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30711] An enzyme complex designated DICER COMPLEX, `dices` the VGAM790 folded precursor RNA into VGAM790 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other



necessary proteins. A probable (over 58%) nucleotide sequence of VGAM790 RNA is designated SEQ ID:3501, and is provided hereinbelow with reference to the sequence listing part.

[30712] VGAM790 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM790 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM790 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[30713] VGAM790 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM790 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM790 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM790 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM790 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30714] The complementary binding of VGAM790 RNA, herein designated VGAM RNA, to host target binding sites on VGAM790 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM790 host target RNA into VGAM790 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30715] It is appreciated that VGAM790 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM790 host target genes. The mRNA of each one of this plurality of VGAM790 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM790 RNA, herein designated VGAM RNA, and which when bound by VGAM790 RNA causes inhibition of translation of respective one or more VGAM790 host target proteins.

[30716] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM790 gene, herein designated VGAM GENE, on one or more VGAM790 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30717] It is yet further appreciated that a function of VGAM790 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM790 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM790 correlate with, and may be deduced from, the identity of the host target genes which VGAM790 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30718] Nucleotide sequences of the VGAM790 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM790 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM790 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM790 are further described hereinbelow with reference to Table 1.

[30719] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM790 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM790 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[30720] As mentioned hereinabove with reference to Fig. 1, a function of VGAM790 gene, herein designated VGAM is inhibition of expression of VGAM790 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM790 correlate with, and may be deduced from, the identity of the target genes which VGAM790 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30721] KIAA0635 (Accession NM\_014645) is a VGAM790 host target gene. KIAA0635 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0635, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0635 BINDING SITE, designated SEQ ID:16056, to the nucleotide sequence of VGAM790 RNA, herein designated VGAM RNA, also designated SEQ ID:3501.

[30722] A function of VGAM790 is therefore inhibition of KIAA0635 (Accession NM\_014645). Accordingly, utilities of VGAM790 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0635. LOC150142 (Accession XM\_086791) is another VGAM790 host target gene. LOC150142 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC150142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150142 BINDING SITE, designated SEQ ID:38850, to the nucleotide sequence of VGAM790 RNA, herein designated VGAM RNA, also designated SEQ ID:3501.

[30723] Another function of VGAM790 is therefore inhibition of LOC150142 (Accession XM\_086791). Accordingly, utilities of VGAM790 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150142. LOC158187 (Accession XM\_098892) is another VGAM790 host target gene. LOC158187 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC158187, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158187 BINDING SITE, designated SEQ ID:41922, to

the nucleotide sequence of VGAM790 RNA, herein designated VGAM RNA, also designated SEQ ID:3501.

[30724] Another function of VGAM790 is therefore inhibition of LOC158187 (Accession XM\_098892). Accordingly, utilities of VGAM790 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158187. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 791 (VGAM791) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30725] VGAM791 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM791 was detected is described hereinabove with reference to Figs. 1–8.

[30726] VGAM791 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM791 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30727] VGAM791 gene encodes a VGAM791 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM791 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM791 precursor RNA is designated SEQ ID:777, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:777 is located at position 6245 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30728] VGAM791 precursor RNA folds onto itself, forming VGAM791 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30729] An enzyme complex designated DICER COMPLEX, `dices` the VGAM791 folded precursor RNA into VGAM791 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short



~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM791 RNA is designated SEQ ID:3502, and is provided hereinbelow with reference to the sequence listing part.

[30730] VGAM791 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM791 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM791 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[30731] VGAM791 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM791 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM791 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM791 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM791 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30732] The complementary binding of VGAM791 RNA, herein designated VGAM RNA, to host target binding sites on VGAM791 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM791 host target RNA into VGAM791 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30733] It is appreciated that VGAM791 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM791 host target genes. The mRNA of each one of this plurality of VGAM791 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM791 RNA, herein designated VGAM RNA, and which when bound by VGAM791 RNA causes inhibition of translation of respective one or more VGAM791 host target proteins.

[30734] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM791 gene, herein designated VGAM GENE, on one or more VGAM791 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[30735] It is yet further appreciated that a function of VGAM791 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM791 correlate with, and may be deduced from, the identity of the host target genes which VGAM791 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30736] Nucleotide sequences of the VGAM791 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM791 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM791 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM791 are further described hereinbelow with reference to Table 1.

[30737] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM791 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM791 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30738] As mentioned hereinabove with reference to Fig. 1, a function of VGAM791 gene, herein designated VGAM is inhibition of expression of VGAM791 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM791 correlate with, and may be deduced from, the identity of the target genes which VGAM791 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30739] S-adenosylhomocysteine Hydrolase (AHCY, Accession NM\_000687) is a VGAM791 host target gene. AHCY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AHCY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AHCY BINDING SITE, designated SEQ ID:6345, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30740] A function of VGAM791 is therefore inhibition of S-

adenosylhomocysteine Hydrolase (AHCY, Accession NM\_000687). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AHCY. Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 2 (CBFA2T2, Accession NM\_005093) is another VGAM791 host target gene. CBFA2T2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CBFA2T2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CBFA2T2 BINDING SITE, designated SEQ ID:11554, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30741] Another function of VGAM791 is therefore inhibition of Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 2 (CBFA2T2, Accession NM\_005093), a gene which is a putative transcription factor. Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBFA2T2. The function of CBFA2T2 and its association with various diseases and clinical conditions, has

been established by previous studies, as described herein above with reference to

VGAM152. Cystathionine-β-synthase (CBS, Accession NM\_000071) is another VGAM791 host target gene. CBS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CBS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CBS BINDING SITE, designated SEQ ID:5516, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30742] Another function of VGAM791 is therefore inhibition of Cystathionine-β-synthase (CBS, Accession NM\_000071). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBS. Ets Variant Gene 3 (ETV3, Accession NM\_005240) is another VGAM791 host target gene. ETV3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ETV3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of ETV3 BINDING SITE, designated SEQ ID:11751, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30743] Another function of VGAM791 is therefore inhibition of Ets Variant Gene 3 (ETV3, Accession NM\_005240), a gene which Member of the ETS oncoprotein family. Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ETV3. The function of ETV3 has been established by previous studies. The ETS oncogene (OMIM Ref. No. 164720) was first described as part of a fusion gene transduced by the avian retrovirus E26. In E26, v-ets and v-myb (OMIM Ref. No. 189990) were fused to a portion of GAG to form the transforming gene. The ETS oncogene family shares a conserved peptide motif called the ETS domain that mediates sequence-specific DNA binding. This motif is unique among transcription factor families. Using partially degenerate oligonucleotides from conserved regions of the ETS domain and the polymerase chain reaction, Klemsz et al. (1994) isolated a new member of the ETS family, designated PE1, from HL60 cells. The PE1 gene was expressed as an approximately 5-kb



transcript in most cell lines tested. Klappacher et al. (2002) described a mechanism in which induction of the ETS repressor METS links terminal differentiation to cell cycle arrest. Using macrophages as a model, they provided evidence that METS blocks RAS (OMIM Ref. No. 190020)-dependent proliferation without inhibiting RAS-dependent expression of cell type-specific genes by selectively replacing ETS activators on the promoters of cell cycle control genes. The antiproliferative effects of METS required its interaction with DP103 (DDX20; 606168), a DEAD box-containing protein that assembles a novel corepressor complex. Functional interactions between the METS/DP103 complex and E2F (see OMIM Ref. No. 189971)/RB (see OMIM Ref. No. 180200) family proteins were also necessary for inhibition of cellular proliferation, suggesting a combinatorial code that directs permanent cell cycle exit during terminal differentiation. Using both in situ hybridization and study of human/hamster cell hybrids, Klemsz et al. (1994) demonstrated that the PE1 gene is located on 1q21-q23.

[30744] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30745] Klappacher, G. W.; Lunyak, V. V.; Sykes, D. B.; Sawka-Verhelle, D.; Sage, J.; Brard, G.; Ngo, S. D.; Gangadharan, D.; Jacks, T.; Kamps, M. P.; Rose, D. W.; Rosenfeld, M. G. : An induced Ets repressor complex regulates growth arrest during terminal macrophage differentiation. Cell 109: 169–180, 2002. ; and

[30746] Klemsz, M.; Hromas, R.; Raskind, W.; Bruno, E.; Hoffman, R. : PE-1, a novel ETS oncogene family member, localizes to chromosome 1q21–q23. Genomics 20: 291–294, 1994.

[30747] Further studies establishing the function and utilities of ETV3 are found in John Hopkins OMIM database record ID 164873, and in cited publications numbered 3141–3142 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Follistatin-like 1 (FSTL1, Accession NM\_007085) is another VGAM791 host target gene. FSTL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FSTL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FSTL1 BINDING SITE, designated SEQ ID:13950, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ

ID:3502.

[30748] Another function of VGAM791 is therefore inhibition of Follistatin-like 1 (FSTL1, Accession NM\_007085), a gene which may modulate the action of some growth factors on cell proliferation and differentiation. Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FSTL1. The function of FSTL1 has been established by previous studies. Using degenerate primers designed against a peptide purified from a rat glioma cell line, Zwijsen et al. (1994) isolated a full-length follistatin-like cDNA (FSTL1), which they called FRP, from a human glioma cDNA library. FSTL1 encodes a deduced 308-amino acid protein with an N-terminal signal peptide of 20 amino acids. FSTL1 contains an FS module, a follistatin-like sequence containing 10 conserved cysteine residues. The number and distribution of the cysteine residues supports the existence of several intramolecular disulfide bridges. Zwijsen et al. (1994) did not detect any membrane-spanning or membrane-associated sequences in the FSTL1 sequence, but they predicted 3 putative N-glycosylation sites and several phosphorylation sites. Under denaturing conditions, Zwijsen et al. (1994) detected several isoforms of FSTL1 with

molecular masses of 40 to 48 kD which differs from the 50- to 55-kD products detected by Tanaka et al. (1998). Tanaka et al. (1998) hypothesized that the difference results from the molecular conditions affected by posttranslational modification. FSTL1 shares greater than 92% amino acid identity with the mouse homolog, known as Fstl or TSC-36, identified as a transforming growth factor-beta-inducible protein by Shibamura et al. (1993). Zwijsen et al. (1994) also noted sequence similarity to follistatin (OMIM Ref. No. 136470) and agrin (OMIM Ref. No. 103320), and could not detect any effect of FSTL1 on the cell growth inhibition of TGF-beta (OMIM Ref. No. 190180). Using Northern blot analysis, Tanaka et al. (1998) detected a broadly expressed 4.4-kb FSTL1 transcript most strongly in the heart, placenta, prostate, ovary, and small intestine. Expression was not detected in peripheral blood leukocytes. Tanaka et al. (1998) constructed synovium expression cDNA libraries made from rheumatoid arthritis (RA; 180300) patient-derived synovial cell mRNA. By screening the libraries by IgG purified from synovial fluids from RA patients, they identified FSTL1. Using immunoblotting analysis, they detected anti-FSTL1 antibodies as more frequent in the synovial fluids

and serum of RA patients than in patients with other systemic rheumatic diseases or in healthy individuals. patients. Immunoprecipitation analysis showed no difference between these groups in the amount of synovial FSTL1 protein, suggesting an elevated turnover in RA.

[30749] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30750] Tanaka, M.; Ozaki, S.; Osakada, F.; Mori, K.; Okubo, M.; Nakao, K. : Cloning of follistatin-related protein as a novel autoantigen in systemic rheumatic diseases. Int. Immun. 10: 1305-1314, 1998. ; and

[30751] Zwijsen, A.; Blockx, H.; van Arnhem, W.; Willems, J.; Fransen, L.; Devos, K.; Raymackers, J.; van de Voorde, A.; Slegers, H. : Characterization of a rat C6 glioma-secreted follistatin-r.

[30752] Further studies establishing the function and utilities of FSTL1 are found in John Hopkins OMIM database record ID 605547, and in cited publications numbered 6399-6401 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. GA (Accession NM\_013267) is another VGAM791 host target gene. GA BINDING SITE is HOST TARGET binding site found in the

5` untranslated region of mRNA encoded by GA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GA BINDING SITE, designated SEQ ID:14935, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30753] Another function of VGAM791 is therefore inhibition of GA (Accession NM\_013267). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GA. Maltase–glucoamylase (alpha–glucosidase) (MGAM, Accession XM\_051351) is another VGAM791 host target gene. MGAM BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MGAM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAM BINDING SITE, designated SEQ ID:35821, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30754] Another function of VGAM791 is therefore inhibition of Maltase–glucoamylase (alpha–glucosidase) (MGAM, Acces–

sion XM\_051351), a gene which plays a role in the final steps of digestion of starch. Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGAM. The function of MGAM has been established by previous studies. Maltase–glucoamylase (MGA; EC 3.2.1.20) is a brush border membrane enzyme that plays a role in the final steps of digestion of starch. Naim et al. (1988) showed that it is synthesized as a single–chain polypeptide precursor, acquires N– and O–linked carbohydrates, and does not undergo intracellular or extracellular proteolytic cleavage. Nichols et al. (1998) purified and partially sequenced the human maltase–glucoamylase protein. By RT–PCR using degenerate oligonucleotides based on the MGA protein sequence, they isolated human small intestine MGA cDNAs. The deduced 1,857–amino acid MGA protein has a putative type II membrane anchor, 2 WIDMNE catalytic sites, which are characteristic of carbohydrate hydrolases such as sucrase–isomaltase (SI; 222900), and 2 glycosyl hydrolase family 31 signature 2 sequences. MGA also has 19 potential N–glycosylation sites and 253 potential O–glycosylation sites. The MGA protein shares 59% sequence identity with SI. RT–PCR de–

tected MGA expression in human small intestine, granulocyte, and kidney but not in salivary gland or pancreas.

[30755] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30756] Naim, H. Y.; Sterchi, E. E.; Lentze, M. J. : Structure, biosynthesis, and glycosylation of human small intestinal maltase–glucoamylase. *J. Biol. Chem.* 263: 19709–19717, 1988. ; and

[30757] Nichols, B. L.; Eldering, J.; Avery, S.; Hahn, D.; Quaroni, A.; Sterchi, E. : Human small intestinal maltase–glucoamylase cDNA cloning: homology to sucrase–isomaltase. *J. Biol. Chem.* 273: 3.

[30758] Further studies establishing the function and utilities of MGAM are found in John Hopkins OMIM database record ID 154360, and in cited publications numbered 12706–12708 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. SH3–domain GRB2–like 1 (SH3GL1, Accession NM\_003025) is another VGAM791 host target gene. SH3GL1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SH3GL1, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SH3GL1 BINDING SITE, designated SEQ ID:8960, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30759] Another function of VGAM791 is therefore inhibition of SH3-domain GRB2-like 1 (SH3GL1, Accession NM\_003025). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SH3GL1. Sorbin and SH3 Domain Containing 1 (SORBS1, Accession NM\_015385) is another VGAM791 host target gene. SORBS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SORBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SORBS1 BINDING SITE, designated SEQ ID:17691, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30760] Another function of VGAM791 is therefore inhibition of Sorbin and SH3 Domain Containing 1 (SORBS1, Accession

NM\_015385), a gene which necessary for cell polarization during vegetative growth. Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SORBS1. The function of SORBS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM475. Tropomodulin 2 (neuronal) (TMOD2, Accession NM\_014548) is another VGAM791 host target gene. TMOD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMOD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMOD2 BINDING SITE, designated SEQ ID:15862, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30761] Another function of VGAM791 is therefore inhibition of Tropomodulin 2 (neuronal) (TMOD2, Accession NM\_014548), a gene which is an actin-capping protein for the slow-growing end of filamentous actin. Accordingly, utilities of VGAM791 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with TMOD2. The function of TMOD2 has been established by previous studies. Watakabe et al. (1996) identified and purified rat NTMOD as a protein that binds to the neuron-specific tropomyosin isoform, Tmbr3. Using degenerate oligonucleotides based on peptide sequences of NTMOD, they cloned an NTMOD cDNA from a rat brain cDNA library. Northern blot and RNase protection analyses detected NTMOD mRNA expression predominantly in brain. Immunofluorescence of primary frontal cortex cell cultures showed that NTMOD is specifically expressed in neurons. By screening a human cerebellar cDNA library with a portion of the rat NTMOD as probe, Cox and Zoghbi (2000) cloned a human NTMOD cDNA, designated TMOD2. TMOD2 encodes a deduced 351-amino acid protein. Northern blot analysis demonstrated restricted expression of TMOD2 in neuronal tissues; an approximately 9.5-kb transcript was seen in all brain regions. Cox and Zoghbi (2000) also cloned the mouse ortholog. Northern blot analysis showed that expression of mouse Tmod2 occurred as early as embryonic day 7 and progressively increased during development.

[30762] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [30763] Watakabe, A.; Kobayashi, R.; Helfman, D. M. : N-tropomodulin: a novel isoform of tropomodulin identified as the major binding protein to brain tropomyosin. J. Cell Sci. 109: 2299–2310, 1996. ; and
- [30764] Cox, P. R.; Zoghbi, H. Y. : Sequencing, expression analysis, and mapping of three unique human tropomodulin genes and their mouse orthologs. Genomics 63: 97–107, 2000.
- [30765] Further studies establishing the function and utilities of TMOD2 are found in John Hopkins OMIM database record ID 602928, and in cited publications numbered 7751–7752 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tumor Necrosis Factor Receptor Superfamily, Member 8 (TNFRSF8, Accession NM\_001243) is another VGAM791 host target gene. TNFRSF8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFRSF8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFRSF8 BINDING SITE,

designated SEQ ID:6912, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30766] Another function of VGAM791 is therefore inhibition of Tumor Necrosis Factor Receptor Superfamily, Member 8 (TNFRSF8, Accession NM\_001243), a gene which regulates gene expression through activation of nf-kappab. Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFRSF8. The function of TNFRSF8 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM154.ATP-binding Cassette, Sub-family A (ABC1), Member 5 (ABCA5, Accession NM\_018672) is another VGAM791 host target gene. ABCA5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ABCA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCA5 BINDING SITE, designated SEQ ID:20747, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ

ID:3502.

[30767] Another function of VGAM791 is therefore inhibition of ATP-binding Cassette, Sub-family A (ABC1), Member 5 (ABCA5, Accession NM\_018672). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCA5. Calsenilin, Presenilin Binding Protein, EF Hand Transcription Factor (CSEN, Accession NM\_013434) is another VGAM791 host target gene. CSEN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSEN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSEN BINDING SITE, designated SEQ ID:15088, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30768] Another function of VGAM791 is therefore inhibition of Calsenilin, Presenilin Binding Protein, EF Hand Transcription Factor (CSEN, Accession NM\_013434). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSEN. DKFZP667O116 (Accession XM\_168586) is an-

other VGAM791 host target gene. DKFZP667O116 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP667O116, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP667O116 BINDING SITE, designated SEQ ID:45264, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30769] Another function of VGAM791 is therefore inhibition of DKFZP667O116 (Accession XM\_168586). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP667O116. FLJ14326 (Accession NM\_032191) is another VGAM791 host target gene. FLJ14326 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14326, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14326 BINDING SITE, designated SEQ ID:25905, to the nucleotide sequence of VGAM791 RNA, herein designated

VGAM RNA, also designated SEQ ID:3502.

[30770] Another function of VGAM791 is therefore inhibition of FLJ14326 (Accession NM\_032191). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14326. FLJ20359 (Accession NM\_017781) is another VGAM791 host target gene. FLJ20359 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20359, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20359 BINDING SITE, designated SEQ ID:19412, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30771] Another function of VGAM791 is therefore inhibition of FLJ20359 (Accession NM\_017781). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20359. FLJ22471 (Accession NM\_025140) is another VGAM791 host target gene. FLJ22471 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22471, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22471 BINDING SITE, designated SEQ ID:24778, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30772] Another function of VGAM791 is therefore inhibition of FLJ22471 (Accession NM\_025140). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22471. KIAA0543 (Accession XM\_044213) is another VGAM791 host target gene. KIAA0543 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0543, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0543 BINDING SITE, designated SEQ ID:34178, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30773] Another function of VGAM791 is therefore inhibition of KIAA0543 (Accession XM\_044213). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0543. KIAA0775 (Accession NM\_014726) is another VGAM791 host target gene. KIAA0775 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0775, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0775 BINDING SITE, designated SEQ ID:16320, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30774] Another function of VGAM791 is therefore inhibition of KIAA0775 (Accession NM\_014726). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0775. KIAA0939 (Accession XM\_030524) is another VGAM791 host target gene. KIAA0939 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0939, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0939 BINDING SITE, designated SEQ ID:31067, to the

nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30775] Another function of VGAM791 is therefore inhibition of KIAA0939 (Accession XM\_030524). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0939. KIAA1054 (Accession XM\_043493) is another VGAM791 host target gene. KIAA1054 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1054, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1054 BINDING SITE, designated SEQ ID:33958, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30776] Another function of VGAM791 is therefore inhibition of KIAA1054 (Accession XM\_043493). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1054. KIAA1155 (Accession XM\_030864) is another VGAM791 host target gene. KIAA1155 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1155 BINDING SITE, designated SEQ ID:31202, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30777] Another function of VGAM791 is therefore inhibition of KIAA1155 (Accession XM\_030864). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1155. Protocadherin 19 (PCDH19, Accession XM\_033173) is another VGAM791 host target gene. PCDH19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDH19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDH19 BINDING SITE, designated SEQ ID:31862, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30778] Another function of VGAM791 is therefore inhibition of

Protocadherin 19 (PCDH19, Accession XM\_033173). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH19. Prefoldin 1 (PFDN1, Accession NM\_002622) is another VGAM791 host target gene. PFDN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PFDN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PFDN1 BINDING SITE, designated SEQ ID:8484, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30779] Another function of VGAM791 is therefore inhibition of Prefoldin 1 (PFDN1, Accession NM\_002622). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PFDN1. Retinoic Acid Induced 16 (RAI16, Accession NM\_022749) is another VGAM791 host target gene. RAI16 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAI16, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAI16 BINDING SITE, designated SEQ ID:22971, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30780] Another function of VGAM791 is therefore inhibition of Retinoic Acid Induced 16 (RAI16, Accession NM\_022749). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAI16. LOC115509 (Accession XM\_056092) is another VGAM791 host target gene. LOC115509 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115509, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115509 BINDING SITE, designated SEQ ID:36365, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30781] Another function of VGAM791 is therefore inhibition of LOC115509 (Accession XM\_056092). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC115509. LOC127281 (Accession XM\_059128) is another VGAM791 host target gene. LOC127281 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC127281, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127281 BINDING SITE, designated SEQ ID:36892, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30782] Another function of VGAM791 is therefore inhibition of LOC127281 (Accession XM\_059128). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127281. LOC130813 (Accession XM\_065904) is another VGAM791 host target gene. LOC130813 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130813, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130813 BINDING SITE, designated SEQ ID:37314, to

the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30783] Another function of VGAM791 is therefore inhibition of LOC130813 (Accession XM\_065904). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130813. LOC145468 (Accession XM\_057874) is another VGAM791 host target gene. LOC145468 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145468, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145468 BINDING SITE, designated SEQ ID:36550, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30784] Another function of VGAM791 is therefore inhibition of LOC145468 (Accession XM\_057874). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145468. LOC150155 (Accession XM\_047977) is another VGAM791 host target gene. LOC150155 BINDING SITE is HOST TARGET binding site found in the 3' un-



translated region of mRNA encoded by LOC150155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150155 BINDING SITE, designated SEQ ID:35092, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30785] Another function of VGAM791 is therefore inhibition of LOC150155 (Accession XM\_047977). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150155. LOC200982 (Accession XM\_117305) is another VGAM791 host target gene. LOC200982 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200982, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200982 BINDING SITE, designated SEQ ID:43378, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30786] Another function of VGAM791 is therefore inhibition of LOC200982 (Accession XM\_117305). Accordingly, utilities

of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200982. LOC204301 (Accession XM\_115306) is another VGAM791 host target gene. LOC204301 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC204301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC204301 BINDING SITE, designated SEQ ID:43096, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30787] Another function of VGAM791 is therefore inhibition of LOC204301 (Accession XM\_115306). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC204301. LOC221968 (Accession XM\_166524) is another VGAM791 host target gene. LOC221968 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221968, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC221968 BINDING SITE, designated SEQ ID:44470, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30788] Another function of VGAM791 is therefore inhibition of LOC221968 (Accession XM\_166524). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221968. LOC253128 (Accession XM\_170726) is another VGAM791 host target gene. LOC253128 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253128, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253128 BINDING SITE, designated SEQ ID:45485, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30789] Another function of VGAM791 is therefore inhibition of LOC253128 (Accession XM\_170726). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253128. LOC254358 (Accession XM\_170771) is another VGAM791 host target gene. LOC254358 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254358, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254358 BINDING SITE, designated SEQ ID:45534, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30790] Another function of VGAM791 is therefore inhibition of LOC254358 (Accession XM\_170771). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254358. LOC254413 (Accession XM\_173141) is another VGAM791 host target gene. LOC254413 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254413, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254413 BINDING SITE, designated SEQ ID:46404, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30791] Another function of VGAM791 is therefore inhibition of

LOC254413 (Accession XM\_173141). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254413. LOC254428 (Accession XM\_170932) is another VGAM791 host target gene. LOC254428 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254428 BINDING SITE, designated SEQ ID:45717, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30792] Another function of VGAM791 is therefore inhibition of LOC254428 (Accession XM\_170932). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254428. LOC254659 (Accession XM\_170822) is another VGAM791 host target gene. LOC254659 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254659, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC254659 BINDING SITE, designated SEQ ID:45601, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30793] Another function of VGAM791 is therefore inhibition of LOC254659 (Accession XM\_170822). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254659. LOC254755 (Accession XM\_173224) is another VGAM791 host target gene. LOC254755 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254755, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254755 BINDING SITE, designated SEQ ID:46489, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30794] Another function of VGAM791 is therefore inhibition of LOC254755 (Accession XM\_173224). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254755. LOC254848 (Accession XM\_173133) is an-

other VGAM791 host target gene. LOC254848 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254848 BINDING SITE, designated SEQ ID:46379, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30795] Another function of VGAM791 is therefore inhibition of LOC254848 (Accession XM\_173133). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254848. LOC51107 (Accession NM\_016022) is another VGAM791 host target gene. LOC51107 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51107, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51107 BINDING SITE, designated SEQ ID:18098, to the nucleotide sequence of VGAM791 RNA, herein designated VGAM RNA, also designated SEQ ID:3502.

[30796] Another function of VGAM791 is therefore inhibition of LOC51107 (Accession NM\_016022). Accordingly, utilities of VGAM791 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51107. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 792 (VGAM792) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30797] VGAM792 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM792 was detected is described hereinabove with reference to Figs. 1–8.

[30798] VGAM792 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM792 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30799] VGAM792 gene encodes a VGAM792 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM792



precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM792 precursor RNA is designated SEQ ID:778, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:778 is located at position 13192 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30800] VGAM792 precursor RNA folds onto itself, forming VGAM792 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30801] An enzyme complex designated DICER COMPLEX, `dices` the VGAM792 folded precursor RNA into VGAM792 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM792 RNA is designated SEQ ID:3503, and is provided hereinbelow with reference to the sequence listing part.

[30802] VGAM792 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM792 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM792 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[30803] VGAM792 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM792 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM792 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM792 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM792 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[30804] The complementary binding of VGAM792 RNA, herein designated VGAM RNA, to host target binding sites on VGAM792 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM792 host target RNA into VGAM792 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30805] It is appreciated that VGAM792 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM792 host target genes. The mRNA of

each one of this plurality of VGAM792 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM792 RNA, herein designated VGAM RNA, and which when bound by VGAM792 RNA causes inhibition of translation of respective one or more VGAM792 host target proteins.

[30806] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM792 gene, herein designated VGAM GENE, on one or more VGAM792 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[30807] It is yet further appreciated that a function of VGAM792 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM792 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM792 correlate with, and may be deduced from, the identity of the host target genes which VGAM792 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30808] Nucleotide sequences of the VGAM792 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM792 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM792 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM792 are further described hereinbelow with reference to Table 1.

[30809] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM792 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM792 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30810] As mentioned hereinabove with reference to Fig. 1, a function of VGAM792 gene, herein designated VGAM is inhibition of expression of VGAM792 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM792 correlate with, and may be deduced from, the identity of the target genes which VGAM792 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30811] EGF-containing Fibulin-like Extracellular Matrix Protein 1 (EFEMP1, Accession NM\_004105) is a VGAM792 host target gene. EFEMP1 BINDING SITE1 and EFEMP1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by EFEMP1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EFEMP1 BINDING SITE1 and EFEMP1 BINDING SITE2, designated SEQ ID:10317 and SEQ ID:20837 respectively, to the nucleotide sequence of VGAM792 RNA, herein designated VGAM RNA, also designated SEQ ID:3503.

[30812] A function of VGAM792 is therefore inhibition of EGF-containing Fibulin-like Extracellular Matrix Protein 1 (EFEMP1, Accession NM\_004105). Accordingly, utilities of VGAM792 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EFEMP1. Solute Carrier Family 6 (neurotransmitter transporter, taurine), Member 6 (SLC6A6, Accession NM\_003043) is another VGAM792 host target gene. SLC6A6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC6A6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC6A6 BINDING SITE, designated SEQ ID:9005, to the nucleotide sequence of VGAM792 RNA, herein designated VGAM RNA, also designated SEQ ID:3503.

[30813] Another function of VGAM792 is therefore inhibition of Solute Carrier Family 6 (neurotransmitter transporter, taurine), Member 6 (SLC6A6, Accession NM\_003043), a gene which transports taurine and other beta-amino acids like beta-alanine. Accordingly, utilities of VGAM792 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC6A6. The function of

SLC6A6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM36. ARHGAP10 (Accession NM\_020824) is another VGAM792 host target gene. ARHGAP10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGAP10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP10 BINDING SITE, designated SEQ ID:21887, to the nucleotide sequence of VGAM792 RNA, herein designated VGAM RNA, also designated SEQ ID:3503.

[30814] Another function of VGAM792 is therefore inhibition of ARHGAP10 (Accession NM\_020824). Accordingly, utilities of VGAM792 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP10. FLJ21126 (Accession XM\_117367) is another VGAM792 host target gene. FLJ21126 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21126, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-



plementarity of the nucleotide sequences of FLJ21126 BINDING SITE, designated SEQ ID:43417, to the nucleotide sequence of VGAM792 RNA, herein designated VGAM RNA, also designated SEQ ID:3503.

[30815] Another function of VGAM792 is therefore inhibition of FLJ21126 (Accession XM\_117367). Accordingly, utilities of VGAM792 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21126. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 793 (VGAM793) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30816] VGAM793 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM793 was detected is described hereinabove with reference to Figs. 1–8.

[30817] VGAM793 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM793 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30818] VGAM793 gene encodes a VGAM793 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM793 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM793 precursor RNA is designated SEQ ID:779, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:779 is located at position 10748 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30819] VGAM793 precursor RNA folds onto itself, forming VGAM793 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30820] An enzyme complex designated DICER COMPLEX, `dices` the VGAM793 folded precursor RNA into VGAM793 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM793 RNA is designated SEQ ID:3504, and is provided hereinbelow with reference to the sequence listing part.

[30821] VGAM793 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM793 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM793 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30822] VGAM793 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM793 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM793 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM793 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM793 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30823] The complementary binding of VGAM793 RNA, herein designated VGAM RNA, to host target binding sites on VGAM793 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM793 host target RNA into VGAM793 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30824] It is appreciated that VGAM793 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM793 host target genes. The mRNA of each one of this plurality of VGAM793 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM793 RNA, herein designated VGAM RNA, and which when bound by VGAM793 RNA causes inhibition of translation of respective one or more VGAM793 host target proteins.

[30825] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM793 gene, herein designated VGAM GENE, on one or more VGAM793 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30826] It is yet further appreciated that a function of VGAM793 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM793 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM793 correlate with, and may be deduced from, the identity of the host target genes which VGAM793 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30827] Nucleotide sequences of the VGAM793 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM793 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM793 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM793 are further described hereinbelow with reference to Table 1.

[30828] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM793 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM793 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30829] As mentioned hereinabove with reference to Fig. 1, a function of VGAM793 gene, herein designated VGAM is inhibition of expression of VGAM793 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM793 correlate with, and may be deduced from, the identity of the target genes which VGAM793 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30830] Myosin, Light Polypeptide Kinase (MYLK, Accession XM\_173098) is a VGAM793 host target gene. MYLK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYLK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYLK BINDING SITE, designated SEQ ID:46357, to the nucleotide sequence of VGAM793 RNA, herein designated VGAM

RNA, also designated SEQ ID:3504.

[30831] A function of VGAM793 is therefore inhibition of Myosin, Light Polypeptide Kinase (MYLK, Accession XM\_173098), a gene which is involved in contraction of smooth muscle. Accordingly, utilities of VGAM793 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYLK. The function of MYLK has been established by previous studies. The contraction of smooth muscle begins with the phosphorylation of the light chain of myosin (e.g., 160781), a reaction catalyzed by myosin light chain kinase that is itself activated by the binding of calcium-calmodulin (see OMIM Ref. No. 114180). This key enzyme in muscle contraction, which exists in both non-muscle and smooth muscle isoforms, has been shown by immunohistology to be present in neurons and glia.

[30832] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30833] Potier, M.-C.; Chelot, E.; Pekarsky, Y.; Gardiner, K.; Rossier, J.; Turnell, W. G. : The human myosin light chain kinase (MLCK) from hippocampus: cloning, sequencing, expression, and localization to 3cen-q21. Genomics 29: 562-570, 1995. ; and



[30834] Watterson, D. M.; Schavocky, J. P.; Guo, L.; Weiss, C.; Chlenski, A.; Shirinsky, V. P.; Van Eldik, L. J.; Haiech, J. : Analysis of the kinase-related protein gene found at human chromo.

[30835] Further studies establishing the function and utilities of MYLK are found in John Hopkins OMIM database record ID 600922, and in cited publications numbered 9958–9963 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DEPC-1 (Accession NM\_139178) is another VGAM793 host target gene. DEPC-1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DEPC-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DEPC-1 BINDING SITE, designated SEQ ID:29192, to the nucleotide sequence of VGAM793 RNA, herein designated VGAM RNA, also designated SEQ ID:3504.

[30836] Another function of VGAM793 is therefore inhibition of DEPC-1 (Accession NM\_139178). Accordingly, utilities of VGAM793 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DEPC-1.

LOC154007 (Accession XM\_087824) is another VGAM793 host target gene. LOC154007 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154007, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154007 BINDING SITE, designated SEQ ID:39450, to the nucleotide sequence of VGAM793 RNA, herein designated VGAM RNA, also designated SEQ ID:3504.

[30837] Another function of VGAM793 is therefore inhibition of LOC154007 (Accession XM\_087824). Accordingly, utilities of VGAM793 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154007. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 794 (VGAM794) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30838] VGAM794 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM794 was detected is described hereinabove with reference to Figs. 1–8.

[30839] VGAM794 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM794 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30840] VGAM794 gene encodes a VGAM794 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM794 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM794 precursor RNA is designated SEQ ID:780, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:780 is located at position 80483 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30841] VGAM794 precursor RNA folds onto itself, forming VGAM794 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30842] An enzyme complex designated DICER COMPLEX, `dices` the VGAM794 folded precursor RNA into VGAM794 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM794 RNA is designated SEQ ID:3505, and is provided hereinbelow with reference to the sequence listing part.

[30843] VGAM794 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM794 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM794 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30844] VGAM794 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM794 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM794 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM794 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM794 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30845] The complementary binding of VGAM794 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM794 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM794 host target RNA into VGAM794 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30846] It is appreciated that VGAM794 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM794 host target genes. The mRNA of each one of this plurality of VGAM794 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM794 RNA, herein designated VGAM RNA, and which when bound by VGAM794 RNA causes inhibition of translation of respective one or more VGAM794 host target proteins.

[30847] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM794 gene, herein designated VGAM GENE, on one or more VGAM794 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30848] It is yet further appreciated that a function of VGAM794 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM794 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM794 correlate with, and may be deduced from, the identity of the host target genes which VGAM794 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30849] Nucleotide sequences of the VGAM794 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM794 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM794 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM794 are further  
described hereinbelow with reference to Table 1.

[30850] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM794 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM794 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[30851] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM794 gene, herein designated VGAM is  
inhibition of expression of VGAM794 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM794 correlate with, and may be deduced  
from, the identity of the target genes which VGAM794  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[30852] Platelet-derived Growth Factor Receptor, Alpha Polypep-  
tide (PDGFRA, Accession NM\_006206) is a VGAM794 host



target gene. PDGFRA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PDGFRA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PDGFRA BINDING SITE, designated SEQ ID:12879, to the nucleotide sequence of VGAM794 RNA, herein designated VGAM RNA, also designated SEQ ID:3505.

[30853] A function of VGAM794 is therefore inhibition of Platelet-derived Growth Factor Receptor, Alpha Polypeptide (PDGFRA, Accession NM\_006206), a gene which this receptor binds platelet-derived growth factor and has a tyrosine-protein kinase activity. Accordingly, utilities of VGAM794 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PDGFRA. The function of PDGFRA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM117. KIAA0222 (Accession NM\_014643) is another VGAM794 host target gene. KIAA0222 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0222, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0222 BINDING SITE, designated SEQ ID:16047, to the nucleotide sequence of VGAM794 RNA, herein designated VGAM RNA, also designated SEQ ID:3505.

[30854] Another function of VGAM794 is therefore inhibition of KIAA0222 (Accession NM\_014643). Accordingly, utilities of VGAM794 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0222. PRO1600 (Accession NM\_014095) is another VGAM794 host target gene. PRO1600 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO1600, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1600 BINDING SITE, designated SEQ ID:15315, to the nucleotide sequence of VGAM794 RNA, herein designated VGAM RNA, also designated SEQ ID:3505.

[30855] Another function of VGAM794 is therefore inhibition of PRO1600 (Accession NM\_014095). Accordingly, utilities of VGAM794 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PRO1600. TEB4 (Accession XM\_027156) is another VGAM794 host target gene. TEB4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TEB4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TEB4 BINDING SITE, designated SEQ ID:30429, to the nucleotide sequence of VGAM794 RNA, herein designated VGAM RNA, also designated SEQ ID:3505.

[30856] Another function of VGAM794 is therefore inhibition of TEB4 (Accession XM\_027156). Accordingly, utilities of VGAM794 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TEB4. LOC125268 (Accession XM\_071960) is another VGAM794 host target gene. LOC125268 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC125268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC125268 BINDING SITE, designated SEQ ID:37452, to the nucleotide se-

quence of VGAM794 RNA, herein designated VGAM RNA, also designated SEQ ID:3505.

[30857] Another function of VGAM794 is therefore inhibition of LOC125268 (Accession XM\_071960). Accordingly, utilities of VGAM794 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125268. LOC220469 (Accession XM\_084334) is another VGAM794 host target gene. LOC220469 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220469, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220469 BINDING SITE, designated SEQ ID:37556, to the nucleotide sequence of VGAM794 RNA, herein designated VGAM RNA, also designated SEQ ID:3505.

[30858] Another function of VGAM794 is therefore inhibition of LOC220469 (Accession XM\_084334). Accordingly, utilities of VGAM794 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220469. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 795 (VGAM795) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30859] VGAM795 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM795 was detected is described hereinabove with reference to Figs. 1–8.

[30860] VGAM795 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM795 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30861] VGAM795 gene encodes a VGAM795 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM795 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM795 precursor RNA is designated SEQ ID:781, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:781 is located at position 88141 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform

virus).

[30862] VGAM795 precursor RNA folds onto itself, forming VGAM795 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30863] An enzyme complex designated DICER COMPLEX, `dices` the VGAM795 folded precursor RNA into VGAM795 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM795 RNA is designated SEQ ID:3506, and is provided hereinbelow with reference to the sequence listing part.

[30864] VGAM795 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM795 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM795 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30865] VGAM795 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM795 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM795 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM795 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM795 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30866] The complementary binding of VGAM795 RNA, herein designated VGAM RNA, to host target binding sites on VGAM795 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM795 host target RNA into VGAM795 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30867] It is appreciated that VGAM795 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM795 host target genes. The mRNA of each one of this plurality of VGAM795 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM795 RNA, herein designated VGAM RNA, and which when bound by VGAM795 RNA causes inhibition of translation of respective one or more VGAM795 host target proteins.



[30868] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM795 gene, herein designated VGAM GENE, on one or more VGAM795 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30869] It is yet further appreciated that a function of VGAM795 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific func-

tions, and accordingly utilities, of VGAM795 correlate with, and may be deduced from, the identity of the host target genes which VGAM795 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30870] Nucleotide sequences of the VGAM795 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM795 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM795 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM795 are further described hereinbelow with reference to Table 1.

[30871] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM795 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM795 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30872] As mentioned hereinabove with reference to Fig. 1, a function of VGAM795 gene, herein designated VGAM is inhibition of expression of VGAM795 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM795 correlate with, and may be deduced from, the identity of the target genes which VGAM795 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30873] Apoptotic Protease Activating Factor (APAF1, Accession NM\_001160) is a VGAM795 host target gene. APAF1 BINDING SITE1 and APAF1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by APAF1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APAF1 BINDING SITE1 and APAF1 BINDING SITE2, designated SEQ ID:6832 and SEQ ID:14871 respectively, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30874] A function of VGAM795 is therefore inhibition of Apoptotic Protease Activating Factor (APAF1, Accession NM\_001160), a gene which functions in the mitochondrial apoptotic pathway that leads to caspase 9 dependent activation of caspase 3. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APAF1. The function of

APAF1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM552.DEK Oncogene (DNA binding) (DEK, Accession NM\_003472) is another VGAM795 host target gene. DEK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DEK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DEK BINDING SITE, designated SEQ ID:9538, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30875] Another function of VGAM795 is therefore inhibition of DEK Oncogene (DNA binding) (DEK, Accession NM\_003472), a gene which interacts in transcriptional regulation and signal transduction. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DEK. The function of DEK has been established by previous studies. By agarose gel electrophoresis analysis of HeLa nuclear extracts, Alexiadis et al. (2000) detected DEK-induced alterations of the superhelical density of DNA in

chromatin in the presence of topoisomerase I (TOP1; 126420) or II (TOP2A; 126430). The change in topology was not observed in naked DNA. SDS-PAGE analysis indicated that DEK does not induce displacement of histones but that histone H2A/H2B (see OMIM Ref. No. 142711) is required for the DEK-mediated change in nucleosomal DNA topology. Agarose gel electrophoresis analysis showed that DEK reduces the efficiency with which chromatin is replicated. Pre-mRNA splicing involves the step-wise assembly of large RNA-protein complexes, termed spliceosomes, that contain small nuclear ribonucleoprotein particles (OMIM Ref. No. snRNPs) and many non-snRNP splicing factors, many of which contain RS domains (i.e., alternating arg/ser residues). Members of the SR protein family have N-terminal RNA recognition motifs and a phosphorylated C-terminal RS domain. Using splicing and immunoprecipitation assays, McGarvey et al. (2000) identified DEK as one of the first components of the splicing complex that remains associated with spliced exons dependent on prior splicing of pre-mRNA. The association is mediated by specific interactions involving SR proteins such as SRM160 (OMIM Ref. No. 605975).

[30876] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [30877] Alexiadis, V.; Waldmann, T.; Andersen, J.; Mann, M.; Knippers, R.; Gruss, C. : The protein encoded by the proto-oncogene DEK changes the topology of chromatin and reduces the efficiency of DNA replication in a chromatin-specific manner. *Genes Dev.* 14: 1308–1312, 2000. ; and
- [30878] McGarvey, T.; Rosonina, E.; McCracken, S.; Li, Q.; Arnaout, R.; Mientjes, E.; Nickerson, J. A.; Awrey, D.; Greenblatt, J.; Grosveld, G.; Blencowe, B. J. : The acute myeloid leukemia-a.
- [30879] Further studies establishing the function and utilities of DEK are found in John Hopkins OMIM database record ID 125264, and in cited publications numbered 2005–2009 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051) is another VGAM795 host target gene. EGLN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGLN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGLN1 BINDING SITE,

designated SEQ ID:22587, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30880] Another function of VGAM795 is therefore inhibition of Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051), a gene which is expressed in the cytoplasm of arterial smooth muscle cells. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN1. The function of EGLN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM216. Early Growth Response 3 (EGR3, Accession XM\_005040) is another VGAM795 host target gene. EGR3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGR3 BINDING SITE, designated SEQ ID:29958, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30881] Another function of VGAM795 is therefore inhibition of

Early Growth Response 3 (EGR3, Accession XM\_005040), a gene which is a putative transcription factor. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGR3. The function of EGR3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM189. Gamma-aminobutyric Acid (GABA) A Receptor, Pi (GABRP, Accession NM\_014211) is another VGAM795 host target gene. GABRP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GABRP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GABRP BINDING SITE, designated SEQ ID:15480, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30882] Another function of VGAM795 is therefore inhibition of Gamma-aminobutyric Acid (GABA) A Receptor, Pi (GABRP, Accession NM\_014211), a gene which mediates neuronal inhibition by binding to the gaba/benzodiazepine receptor and opening an integral chloride channel. Accordingly,



utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GABRP. The function of GABRP has been established by previous studies. GABA is the major inhibitory neurotransmitter in the mammalian central nervous system and acts by binding to GABA-A receptors (see OMIM Ref. No. 137192). By searching a human EST database with a GABA-A receptor consensus sequence, Hedblom and Kirkness (1997) identified a cDNA encoding GABRP. Sequence analysis revealed that GABRP represented a novel class of GABA-A receptor subunits, being 30 to 40% identical to the 5 subunit classes previously identified. Northern blot analysis showed that the 3.3-kb GABRP mRNA was expressed in several tissues, with particular abundance in the uterus. Hedblom and Kirkness (1997) also cloned cDNAs encoding the rat GABRP homolog. The predicted 440-amino acid sequence of human GABRP is 93% identical to that of rat Gabrp. Expression of human GABRP in mammalian cells indicated that GABRP can combine with other GABA-A receptor subunits and alter the sensitivity of recombinant receptors to modulatory agents such as the steroid pregnanolone. In a review of GABA-A receptors, Whiting et al. (1999) stated that the GABRP gene

maps to 5q32–q33.

[30883] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30884] Hedblom, E.; Kirkness, E. F. : A novel class of GABA–A receptor subunit in tissues of the reproductive system. J. Biol. Chem. 272: 15346–15350, 1997. ; and

[30885] Whiting, P. J.; Bonnert, T. P.; McKernan, R. M.; Farrar, S.; le Bourdelles, B.; Heavens, R. P.; Smith, D. W.; Hewson, L.; Rigby, M. R.; Sirinathsinghji, D. J. S.; Thompson, S. A.; Waffo.

[30886] Further studies establishing the function and utilities of GABRP are found in John Hopkins OMIM database record ID 602729, and in cited publications numbered 8591 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. MTERF (Accession NM\_006980) is another VGAM795 host target gene. MTERF BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MTERF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTERF BINDING SITE, designated SEQ

ID:13842, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30887] Another function of VGAM795 is therefore inhibition of MTERF (Accession NM\_006980), a gene which plays a central role in attenuating transcription between the 16S ribosomal RNA and the tRNA-leu genes in the heavy strand of mitochondrial DNA. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTERF. The function of MTERF has been established by previous studies. The mitochondrial transcription termination factor, or MTERF, plays a central role in attenuating transcription between the 16S ribosomal RNA (OMIM Ref. No. 561010) and the tRNA-leu (OMIM Ref. No. 590050) genes in the heavy strand of mitochondrial DNA, and therefore is part of the regulatory system that allows high levels of ribosomal RNA expression relative to downstream genes. From HeLa cells, Daga et al. (1993) purified 2 related 34-kD polypeptides that had MTERF activity. Fernandez-Silva et al. (1997) cloned the MTERF cDNA by RT-PCR of HeLa cell mRNA using primers derived from peptide sequences of the purified protein. The cDNA encoded a predicted

399-amino acid protein containing a mitochondrial targeting sequence. The mature MTERF protein is 342 amino acids long and contains 3 leucine zipper and 2 basic domains. Mutational analysis showed that all of these domains are necessary for DNA binding, and that the 2 basic domains are involved in directly binding MTERF to its target DNA sequence. Fernandez-Silva et al. (1997) showed that MTERF binds to DNA as a monomer.

[30888] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30889] Daga, A.; Micol, V.; Hess, D.; Aebersold, R.; Attardi, G. : Molecular characterization of the transcription termination factor from human mitochondria. J. Biol. Chem. 268: 8123-8130, 1993. ; and

[30890] Fernandez-Silva, P.; Martinez-Azorin, F.; Micol, V.; Attardi, G. : The human mitochondrial transcription termination factor (mTERF) is a multizipper protein but binds to DNA as a monomer.

[30891] Further studies establishing the function and utilities of MTERF are found in John Hopkins OMIM database record ID 602318, and in cited publications numbered 6299-6301 listed in the bibliography section hereinbelow,

which are also hereby incorporated by reference. Protein Kinase, CAMP-dependent, Catalytic, Beta (PRKACB, Accession NM\_002731) is another VGAM795 host target gene. PRKACB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKACB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKACB BINDING SITE, designated SEQ ID:8604, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30892] Another function of VGAM795 is therefore inhibition of Protein Kinase, CAMP-dependent, Catalytic, Beta (PRKACB, Accession NM\_002731), a gene which is the catalytic beta subunit of cAMP-dependent protein kinase (PKA). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKACB. The function of PRKACB has been established by previous studies. Most of the effects of cAMP in the eukaryotic cell are mediated through the phosphorylation of target proteins on serine or threonine residues by the cAMP-dependent protein kinase (EC 2.7.1.37). The

inactive cAMP-dependent protein kinase is a tetramer composed of 2 regulatory and 2 catalytic subunits. The cooperative binding of 4 molecules of cAMP dissociates the enzyme in a regulatory subunit dimer and 2 free active catalytic subunits. In the human, 4 different regulatory subunits (PRKAR1A, 188830; PRKAR1B, 176911; PRKAR2A, 176910; and PRKAR2B, 176912) and 3 catalytic subunits (PRKACA; PRKACB, 176892; and PRKACG 176893) have been identified. Animal model experiments lend further support to the function of PRKACB. The intracellular second messenger cAMP affects cell physiology by directly interacting with effector molecules that include cyclic nucleotide-gated ion channels, cAMP-regulated G protein exchange factors, and cAMP-dependent protein kinases (PKA). Two catalytic subunits, C-alpha (OMIM Ref. No. PRKACA) and C-beta (OMIM Ref. No. PRKACB), are expressed in the mouse and mediate the effects of PKA. Skalhogg et al. (2002) generated a null mutation in the major catalytic subunit of PKA, C-alpha, and observed early postnatal lethality in the majority of C-alpha knockout mice. Surprisingly, a small percentage of C-alpha knockout mice, although runted, survived to adulthood. This growth retardation was not due to decreased GH

(OMIM Ref. No. 139250) production but did correlate with a reduction in IGF1 (OMIM Ref. No. 147440) mRNA in the liver and diminished production of the major urinary proteins in kidney. In these animals, compensatory increases in C-beta levels occurred in brain whereas many tissues, including skeletal muscle, heart, and sperm, contained less than 10% of the normal PKA activity. Analysis of sperm in C-alpha knockout males revealed that spermatogenesis progressed normally but that mature sperm had defective forward motility

[30893] It is appreciated that the abovementioned animal model for PRKACB is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[30894] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30895] Skalhegg, B. S.; Huang, Y.; Su, T.; Idzerda, R. L.; McKnight, G. S.; Burton, K. A. : Mutation of the C-alpha subunit of PKA leads to growth retardation and sperm dysfunction. Molec. Endocr. 16: 630-639, 2002. ; and

[30896] Tasken, K.; Solberg, R.; Zhao, Y.; Hansson, V.; Jahnsen, T.; Siciliano, M. J. : The gene encoding the catalytic subunit

C-alpha of cAMP-dependent protein kinase (locus PRKACA) localize.

[30897] Further studies establishing the function and utilities of PRKACB are found in John Hopkins OMIM database record ID 176892, and in cited publications numbered 11263 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Kinase, Lysine Deficient 3 (PRKWINK3, Accession XM\_029183) is another VGAM795 host target gene. PRKWINK3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKWINK3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKWINK3 BINDING SITE, designated SEQ ID:30856, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30898] Another function of VGAM795 is therefore inhibition of Protein Kinase, Lysine Deficient 3 (PRKWINK3, Accession XM\_029183). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKWINK3. RAB30, Member RAS Oncogene Family (RAB30, Accession NM\_014488) is



another VGAM795 host target gene. RAB30 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB30, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB30 BINDING SITE, designated SEQ ID:15833, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30899] Another function of VGAM795 is therefore inhibition of RAB30, Member RAS Oncogene Family (RAB30, Accession NM\_014488), a gene which is a GTP-binding protein. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB30. The function of RAB30 has been established by previous studies. Chen et al. (1996) isolated a cDNA encoding RAB30, a small GTP-binding protein of the RAB family, from a human melanocyte cDNA library and from melanoma cells. The deduced 203-amino acid RAB30 protein shares minimal homology with previously documented GTPases. Northern blot analysis detected RAB30 transcripts ranging from 1.7 to 11 kb in most tissues tested. By somatic cell hybrid analysis, Chen et al.

(1996) mapped the RAB30 gene to chromosome 11. Scott (2001) localized the RAB30 gene to 11q12–q14 based on sequence similarity between the RAB30 sequence (GenBank U57092) and chromosome 11 clones (GenBank AP000893 and AP000905).

[30900] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30901] Chen, D.; Guo, J.; Miki, T.; Tachibana, M.; Gahl, W. A. : Molecular cloning of two novel rab genes from human melanocytes. Gene 174: 129–134, 1996. ; and

[30902] Scott, A. F. : Personal Communication. Baltimore, Md., 2/26/2001.

[30903] Further studies establishing the function and utilities of RAB30 are found in John Hopkins OMIM database record ID 605693, and in cited publications numbered 6469 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Retinoblastoma 1 (including osteosarcoma) (RB1, Accession XM\_165641) is another VGAM795 host target gene. RB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND–

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RB1 BINDING SITE, designated SEQ ID:43706, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30904] Another function of VGAM795 is therefore inhibition of Retinoblastoma 1 (including osteosarcoma) (RB1, Accession XM\_165641), a gene which probably acts as a regulator of other genes. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RB1. The function of RB1 has been established by previous studies. Retinoblastoma (RB) is an embryonic neoplasm of retinal origin. It almost always presents in early childhood and is often bilateral. Spontaneous regression (OMIM Ref. No. 'cure') occurs in some cases. Connolly et al. (1983) reported a 4-generation family with 3 patterns of expression of the retinoblastoma gene: frank retinoblastoma, unilateral or bilateral; retinoma; and no visible retinal pathology except for 'normal degeneration' with age. ('Paving stone degeneration' of the type observed in 2 of 3 RB carriers, aged 49 and 59, is said by Duane (1980) to occur in about 20% of the adult population.) Gallie and Phillips (1982) described

benign lesions in the retina in retinoblastoma patients. The distinctive characteristics of these lesions, referred to by the authors as retinomas, included a translucent, grayish retinal mass protruding into the vitreous, 'cottage-cheese' calcification in 75%, and retinal pigment epithelial migration and proliferation in 60%. They suggested that retinomas represent not the heterozygous state postulated by the Knudson 2-stage model of carcinogenesis but rather the homozygous state occurring in differentiated cell(s). Gallie et al. (1982) suggested that retinomas represent either spontaneous regression of a retinoblastoma or a benign manifestation of the RB gene. Animal model experiments lend further support to the function of RB1. Windle et al. (1990) created transgenic mice by microinjecting fertilized ova with a chimeric gene containing the protein coding region of the SV40 T antigen (Tag) driven by the promoter of the luteinizing hormone beta-subunit gene. One of the male founders developed bilateral retinoblastomas at about age 5 months. The phenotype was heritable with complete penetrance in transgenic offspring in whom the tumors were first observed at about 2 months. Windle et al. (1990) demonstrated specific association between p105(Rb) and T antigen in mouse

retinoblastoma tumor cells. Thus, evidence is provided for oncogenesis due to the ocular-specific expression of an Rb-binding oncoprotein that can functionally inactivate the Rb protein.

[30905] It is appreciated that the abovementioned animal model for RB1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[30906] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30907] Connolly, M. J.; Payne, R. H.; Johnson, G.; Gallie, B. L.; Alderdice, P. W.; Marshall, W. H.; Lawton, R. D. : Familial, EsD-linked, retinoblastoma with reduced penetrance and variable expressivity. Hum. Genet. 65: 122-124, 1983. ; and

[30908] Gallie, B. L.; Ellsworth, R. M.; Abramson, D. M.; Phillips, R. A. : Retinoma: spontaneous regression of retinoblastoma or benign manifestation of the mutation? Brit. J. Cancer 45: 513-5.

[30909] Further studies establishing the function and utilities of RB1 are found in John Hopkins OMIM database record ID 180200, and in cited publications numbered

11148–11159, 10077–10078, 43, 82–87, 2358–2378, 4980–2384, 705–711, 4714–715, 3239–730, 5644–5656, 16 and 5657–5664 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transforming Growth Factor, Beta Receptor III (betaglycan, 300kDa) (TGFB3, Accession NM\_003243) is another VGAM795 host target gene. TGFB3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TGFB3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TGFB3 BINDING SITE, designated SEQ ID:9252, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30910] Another function of VGAM795 is therefore inhibition of Transforming Growth Factor, Beta Receptor III (betaglycan, 300kDa) (TGFB3, Accession NM\_003243), a gene which involves in capturing and retaining TGF-beta for presentation to the signaling receptors. Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TGFB3. The function of TGFB3 and its association with various

diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM139.APCL (Accession NM\_005883) is another VGAM795 host target gene. APCL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APCL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APCL BINDING SITE, designated SEQ ID:12499, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30911] Another function of VGAM795 is therefore inhibition of APCL (Accession NM\_005883). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APCL. Cat Eye Syndrome Chromosome Region, Candidate 7 (CECR7, Accession XM\_086803) is another VGAM795 host target gene. CECR7 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CECR7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of CECR7 BINDING SITE, designated SEQ ID:38882, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30912] Another function of VGAM795 is therefore inhibition of Cat Eye Syndrome Chromosome Region, Candidate 7 (CECR7, Accession XM\_086803). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CECR7. FHX (Accession NM\_018416) is another VGAM795 host target gene. FHX BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FHX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FHX BINDING SITE, designated SEQ ID:20459, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30913] Another function of VGAM795 is therefore inhibition of FHX (Accession NM\_018416). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FHX.



FLJ10079 (Accession XM\_012540) is another VGAM795 host target gene. FLJ10079 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10079, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10079 BINDING SITE, designated SEQ ID:30217, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30914] Another function of VGAM795 is therefore inhibition of FLJ10079 (Accession XM\_012540). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10079. FLJ20371 (Accession NM\_017791) is another VGAM795 host target gene. FLJ20371 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20371, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20371 BINDING SITE, designated SEQ ID:19425, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3506.

[30915] Another function of VGAM795 is therefore inhibition of FLJ20371 (Accession NM\_017791). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20371. FLJ22408 (Accession NM\_024794) is another VGAM795 host target gene. FLJ22408 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ22408, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22408 BINDING SITE, designated SEQ ID:24174, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30916] Another function of VGAM795 is therefore inhibition of FLJ22408 (Accession NM\_024794). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22408. FLJ22471 (Accession NM\_025140) is another VGAM795 host target gene. FLJ22471 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22471, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22471 BINDING SITE, designated SEQ ID:24779, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30917] Another function of VGAM795 is therefore inhibition of FLJ22471 (Accession NM\_025140). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22471. Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445) is another VGAM795 host target gene. GRIN3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRIN3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRIN3A BINDING SITE, designated SEQ ID:28534, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30918] Another function of VGAM795 is therefore inhibition of Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A

(GRIN3A, Accession NM\_133445). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRIN3A. KIAA0286 (Accession XM\_043118) is another VGAM795 host target gene. KIAA0286 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0286, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0286 BINDING SITE, designated SEQ ID:33908, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30919] Another function of VGAM795 is therefore inhibition of KIAA0286 (Accession XM\_043118). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0286. KIAA0471 (Accession NM\_014857) is another VGAM795 host target gene. KIAA0471 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0471, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA0471 BINDING SITE, designated SEQ ID:16917, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30920] Another function of VGAM795 is therefore inhibition of KIAA0471 (Accession NM\_014857). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0471. KIAA0523 (Accession XM\_041964) is another VGAM795 host target gene. KIAA0523 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0523, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0523 BINDING SITE, designated SEQ ID:33649, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30921] Another function of VGAM795 is therefore inhibition of KIAA0523 (Accession XM\_041964). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0523. KIAA0560 (Accession XM\_029045) is another

VGAM795 host target gene. KIAA0560 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0560, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0560 BINDING SITE, designated SEQ ID:30839, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30922] Another function of VGAM795 is therefore inhibition of KIAA0560 (Accession XM\_029045). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0560. KIAA1069 (Accession XM\_042635) is another VGAM795 host target gene. KIAA1069 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1069, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1069 BINDING SITE, designated SEQ ID:33727, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30923] Another function of VGAM795 is therefore inhibition of KIAA1069 (Accession XM\_042635). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1069. Neurexophilin 3 (NXPH3, Accession XM\_037847) is another VGAM795 host target gene. NXPH3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NXPH3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NXPH3 BINDING SITE, designated SEQ ID:32724, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30924] Another function of VGAM795 is therefore inhibition of Neurexophilin 3 (NXPH3, Accession XM\_037847). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NXPH3. PFTK1 Protein Kinase 1 (PFTK1, Accession NM\_012395) is another VGAM795 host target gene. PFTK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PFTK1,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PFTK1 BINDING SITE, designated SEQ ID:14755, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30925] Another function of VGAM795 is therefore inhibition of PFTK1 Protein Kinase 1 (PFTK1, Accession NM\_012395). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PFTK1. PRO2893 (Accession NM\_018634) is another VGAM795 host target gene. PRO2893 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PRO2893, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2893 BINDING SITE, designated SEQ ID:20705, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30926] Another function of VGAM795 is therefore inhibition of PRO2893 (Accession NM\_018634). Accordingly, utilities of



VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2893. ZFP (Accession NM\_018651) is another VGAM795 host target gene. ZFP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZFP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFP BINDING SITE, designated SEQ ID:20721, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30927] Another function of VGAM795 is therefore inhibition of ZFP (Accession NM\_018651). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFP. LOC124599 (Accession XM\_064218) is another VGAM795 host target gene. LOC124599 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC124599, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124599 BINDING SITE, designated SEQ ID:37258, to the nucleotide se-

quence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30928] Another function of VGAM795 is therefore inhibition of LOC124599 (Accession XM\_064218). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC124599. LOC145622 (Accession XM\_085186) is another VGAM795 host target gene. LOC145622 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145622, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145622 BINDING SITE, designated SEQ ID:37909, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30929] Another function of VGAM795 is therefore inhibition of LOC145622 (Accession XM\_085186). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145622. LOC148479 (Accession XM\_086204) is another VGAM795 host target gene. LOC148479 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC148479, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148479 BINDING SITE, designated SEQ ID:38544, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30930] Another function of VGAM795 is therefore inhibition of LOC148479 (Accession XM\_086204). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148479. LOC151996 (Accession XM\_098151) is another VGAM795 host target gene. LOC151996 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151996, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151996 BINDING SITE, designated SEQ ID:41418, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30931] Another function of VGAM795 is therefore inhibition of LOC151996 (Accession XM\_098151). Accordingly, utilities

of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151996. LOC152674 (Accession XM\_098251) is another VGAM795 host target gene. LOC152674 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152674, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152674 BINDING SITE, designated SEQ ID:41540, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30932] Another function of VGAM795 is therefore inhibition of LOC152674 (Accession XM\_098251). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152674. LOC154743 (Accession XM\_088029) is another VGAM795 host target gene. LOC154743 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154743, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC154743 BINDING SITE, designated SEQ ID:39482, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30933] Another function of VGAM795 is therefore inhibition of LOC154743 (Accession XM\_088029). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154743. LOC163231 (Accession XM\_092094) is another VGAM795 host target gene. LOC163231 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163231, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163231 BINDING SITE, designated SEQ ID:40102, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30934] Another function of VGAM795 is therefore inhibition of LOC163231 (Accession XM\_092094). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163231. LOC200845 (Accession XM\_114305) is another VGAM795 host target gene. LOC200845 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200845, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200845 BINDING SITE, designated SEQ ID:42865, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30935] Another function of VGAM795 is therefore inhibition of LOC200845 (Accession XM\_114305). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200845. LOC219700 (Accession XM\_167570) is another VGAM795 host target gene. LOC219700 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219700 BINDING SITE, designated SEQ ID:44703, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30936] Another function of VGAM795 is therefore inhibition of

LOC219700 (Accession XM\_167570). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219700. LOC221468 (Accession NM\_145316) is another VGAM795 host target gene. LOC221468 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221468, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221468 BINDING SITE, designated SEQ ID:29828, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30937] Another function of VGAM795 is therefore inhibition of LOC221468 (Accession NM\_145316). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221468. LOC254042 (Accession XM\_171022) is another VGAM795 host target gene. LOC254042 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254042, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC254042 BINDING SITE, designated SEQ ID:45792, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30938] Another function of VGAM795 is therefore inhibition of LOC254042 (Accession XM\_171022). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254042. LOC90075 (Accession XM\_028742) is another VGAM795 host target gene. LOC90075 BINDING SITE1 and LOC90075 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC90075, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90075 BINDING SITE1 and LOC90075 BINDING SITE2, designated SEQ ID:30738 and SEQ ID:30740 respectively, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30939] Another function of VGAM795 is therefore inhibition of LOC90075 (Accession XM\_028742). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with LOC90075. LOC90982 (Accession XM\_035332) is another VGAM795 host target gene. LOC90982 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC90982, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90982 BINDING SITE, designated SEQ ID:32235, to the nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30940] Another function of VGAM795 is therefore inhibition of LOC90982 (Accession XM\_035332). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90982. LOC92391 (Accession XM\_044793) is another VGAM795 host target gene. LOC92391 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC92391, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92391 BINDING SITE, designated SEQ ID:34274, to the

nucleotide sequence of VGAM795 RNA, herein designated VGAM RNA, also designated SEQ ID:3506.

[30941] Another function of VGAM795 is therefore inhibition of LOC92391 (Accession XM\_044793). Accordingly, utilities of VGAM795 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92391. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 796 (VGAM796) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30942] VGAM796 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM796 was detected is described hereinabove with reference to Figs. 1–8.

[30943] VGAM796 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM796 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30944] VGAM796 gene encodes a VGAM796 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM796 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM796 precursor RNA is designated SEQ ID:782, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:782 is located at position 85864 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30945] VGAM796 precursor RNA folds onto itself, forming VGAM796 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30946] An enzyme complex designated DICER COMPLEX, `dices` the VGAM796 folded precursor RNA into VGAM796 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM796 RNA is designated SEQ ID:3507, and is provided hereinbelow with reference to the sequence listing part.

[30947] VGAM796 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM796 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM796 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30948] VGAM796 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM796 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM796 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM796 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM796 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[30949] The complementary binding of VGAM796 RNA, herein designated VGAM RNA, to host target binding sites on VGAM796 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM796 host target RNA into VGAM796 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30950] It is appreciated that VGAM796 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM796 host target genes. The mRNA of each one of this plurality of VGAM796 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM796 RNA, herein designated VGAM RNA, and which when bound by VGAM796 RNA causes inhibition of translation of respective one or more VGAM796 host target proteins.

[30951] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM796 gene, herein designated VGAM GENE, on one or more VGAM796 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[30952] It is yet further appreciated that a function of VGAM796 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM796 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM796 correlate with, and may be deduced from, the identity of the host target genes which VGAM796 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30953] Nucleotide sequences of the VGAM796 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM796 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM796 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM796 are further described hereinbelow with reference to Table 1.

[30954] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM796 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM796 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30955] As mentioned hereinabove with reference to Fig. 1, a function of VGAM796 gene, herein designated VGAM is inhibition of expression of VGAM796 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM796 correlate with, and may be deduced from, the identity of the target genes which VGAM796 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30956] FLJ10842 (Accession NM\_018238) is a VGAM796 host target gene. FLJ10842 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10842, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10842 BINDING SITE, designated SEQ ID:20186, to the nucleotide sequence of VGAM796 RNA, herein designated VGAM RNA, also designated SEQ ID:3507.



[30957] A function of VGAM796 is therefore inhibition of FLJ10842 (Accession NM\_018238). Accordingly, utilities of VGAM796 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10842. LOC202309 (Accession XM\_117375) is another VGAM796 host target gene. LOC202309 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202309, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202309 BINDING SITE, designated SEQ ID:43421, to the nucleotide sequence of VGAM796 RNA, herein designated VGAM RNA, also designated SEQ ID:3507.

[30958] Another function of VGAM796 is therefore inhibition of LOC202309 (Accession XM\_117375). Accordingly, utilities of VGAM796 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202309. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 797 (VGAM797) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[30959] VGAM797 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM797 was detected is described hereinabove with reference to Figs. 1–8.

[30960] VGAM797 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM797 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30961] VGAM797 gene encodes a VGAM797 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM797 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM797 precursor RNA is designated SEQ ID:783, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:783 is located at position 100499 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30962] VGAM797 precursor RNA folds onto itself, forming

VGAM797 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30963] An enzyme complex designated DICER COMPLEX, `dices` the VGAM797 folded precursor RNA into VGAM797 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM797 RNA is designated SEQ ID:3508, and is provided hereinbelow with reference to the sequence listing part.

[30964] VGAM797 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM797 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM797 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30965] VGAM797 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM797 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM797 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM797 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM797 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[30966] The complementary binding of VGAM797 RNA, herein designated VGAM RNA, to host target binding sites on VGAM797 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM797 host target RNA into VGAM797 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[30967] It is appreciated that VGAM797 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM797 host target genes. The mRNA of each one of this plurality of VGAM797 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM797 RNA, herein designated VGAM RNA, and which when bound by VGAM797 RNA causes inhibition of translation of respective one or more VGAM797 host target proteins.

[30968] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM797 gene, herein designated VGAM GENE, on one or more VGAM797 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[30969] It is yet further appreciated that a function of VGAM797 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM797 correlate with, and may be deduced from, the identity of the host

target genes which VGAM797 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[30970] Nucleotide sequences of the VGAM797 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM797 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM797 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM797 are further described hereinbelow with reference to Table 1.

[30971] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM797 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM797 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[30972] As mentioned hereinabove with reference to Fig. 1, a function of VGAM797 gene, herein designated VGAM is inhibition of expression of VGAM797 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM797 correlate with, and may be deduced from, the identity of the target genes which VGAM797

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[30973] Endothelin Receptor Type A (EDNRA, Accession XM\_034331) is a VGAM797 host target gene. EDNRA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EDNRA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EDNRA BINDING SITE, designated SEQ ID:32058, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30974] A function of VGAM797 is therefore inhibition of Endothelin Receptor Type A (EDNRA, Accession XM\_034331), a gene which binds endothelins, and induces intracellular calcium flux and arachidonic acid accumulation. Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EDNRA. The function of EDNRA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM441. Estrogen-related Receptor Gamma (ESRRG, Accession XM\_039053) is another



VGAM797 host target gene. ESRRG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESRRG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRG BINDING SITE, designated SEQ ID:32995, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30975] Another function of VGAM797 is therefore inhibition of Estrogen-related Receptor Gamma (ESRRG, Accession XM\_039053), a gene which Estrogen-related receptor gamma. Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESRRG. The function of ESRRG and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM359. GTP Cyclohydrolase 1 (dopa-responsive dystonia) (GCH1, Accession NM\_000161) is another VGAM797 host target gene. GCH1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GCH1, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GCH1 BINDING SITE, designated SEQ ID:5668, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30976] Another function of VGAM797 is therefore inhibition of GTP Cyclohydrolase 1 (dopa-responsive dystonia) (GCH1, Accession NM\_000161). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GCH1. Neuroligin 1 (NLGN1, Accession NM\_014932) is another VGAM797 host target gene. NLGN1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NLGN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NLGN1 BINDING SITE, designated SEQ ID:17231, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30977] Another function of VGAM797 is therefore inhibition of Neuroligin 1 (NLGN1, Accession NM\_014932), a gene which may trigger the de novo formation of presynaptic

structure. Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NLGN1. The function of NLGN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM659. Regulatory Factor X-associated Protein (RFXAP, Accession NM\_000538) is another VGAM797 host target gene. RFXAP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RFXAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RFXAP BINDING SITE, designated SEQ ID:6136, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30978] Another function of VGAM797 is therefore inhibition of Regulatory Factor X-associated Protein (RFXAP, Accession NM\_000538), a gene which binds to the x-box of mhc ii promoters and is a transcriptional regulator. Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with RFXAP. The function of RFXAP has been established by previous studies. Yanagisawa et al. (2000) isolated and analyzed a gene that shares a notable motif with DRPLA, namely that of arginine–glutamic acid (RE) dipeptide repeats. The gene that was isolated, designated RERE, has an open reading frame of 1,566 amino acids, of which the C-terminal portion has 67% homology to DRPLA, whereas the N-terminal portion is distinctive. RERE also contains arginine–aspartic acid (RD) dipeptide repeats and putative nuclear localization signal sequences, but no polyglutamine tracts. Northern blot analysis detected 2 RERE transcripts: one of 9 kb, expressed exclusively in pancreas and testis; and one of 7 kb, expressed most strongly in skeletal muscle with weaker expression in other tissues tested, including brain. The RERE protein migrated at an apparent molecular weight of 212 kD in SDS–PAGE. An RERE fusion protein localized predominantly in the nucleus. Immunoprecipitation and in vitro binding assays demonstrated that the DRPLA and RERE proteins bind each other, which is facilitated by one of the RE repeats, and that extension of the DRPLA polyglutamine tract enhances the binding. By study of a YAC spanning a translocation/duplication breakpoint within the minimally defined loss of

heterozygosity region at 1p36.2–p36.1 in a neuroblastoma cell line, Amler et al. (2000) identified the RERE gene, which they designated DNB1/ARP (deleted in neuroblastoma–1/atrophin–related protein

[30979] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[30980] Amler, L. C.; Bauer, A.; Corvi, R.; Dihlmann, S.; Praml, C.; Cavenee, W. K.; Schwab, M.; Hampton, G. M. : Identification and characterization of novel genes located at the t(1;15)(p36.2;q24) translocation breakpoint in the neuroblastoma cell line NGP. Genomics 64: 195–202, 2000. ; and

[30981] Yanagisawa, H.; Bundo, M.; Miyashita, T.; Okamura–Oho, Y.; Tadokoro, K.; Tokunaga, K.; Yamada, M. : Protein binding of a DRPLA family through arginine–glutamic acid dipeptide repeats i.

[30982] Further studies establishing the function and utilities of RFXAP are found in John Hopkins OMIM database record ID 601861, and in cited publications numbered 5800–5801, 8317–580 and 6077 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Serine Racemase (SRR, Accession

NM\_021947) is another VGAM797 host target gene. SRR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SRR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRR BINDING SITE, designated SEQ ID:22473, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30983] Another function of VGAM797 is therefore inhibition of Serine Racemase (SRR, Accession NM\_021947). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRR. Src Homology Three (SH3) and Cysteine Rich Domain (STAC, Accession NM\_003149) is another VGAM797 host target gene. STAC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STAC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAC BINDING SITE, designated SEQ ID:9120, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3508.

[30984] Another function of VGAM797 is therefore inhibition of Src Homology Three (SH3) and Cysteine Rich Domain (STAC, Accession NM\_003149), a gene which is probably involved in a neuron-specific signal transduction. Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAC. The function of STAC and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM331.FLJ10922 (Accession NM\_018273) is another VGAM797 host target gene. FLJ10922 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10922, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10922 BINDING SITE, designated SEQ ID:20256, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30985] Another function of VGAM797 is therefore inhibition of FLJ10922 (Accession NM\_018273). Accordingly, utilities of

VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10922. KIAA1900 (Accession XM\_055299) is another VGAM797 host target gene. KIAA1900 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1900, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1900 BINDING SITE, designated SEQ ID:36261, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30986] Another function of VGAM797 is therefore inhibition of KIAA1900 (Accession XM\_055299). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1900. MEGF11 (Accession NM\_032445) is another VGAM797 host target gene. MEGF11 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MEGF11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEGF11



BINDING SITE, designated SEQ ID:26206, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30987] Another function of VGAM797 is therefore inhibition of MEGF11 (Accession NM\_032445). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEGF11. Rab11-FIP2 (Accession NM\_014904) is another VGAM797 host target gene. Rab11-FIP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by Rab11-FIP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Rab11-FIP2 BINDING SITE, designated SEQ ID:17100, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30988] Another function of VGAM797 is therefore inhibition of Rab11-FIP2 (Accession NM\_014904). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rab11-FIP2. Ring Finger Protein (C3HC4 type) 8 (RNF8, Accession NM\_003958) is another VGAM797 host target

gene. RNF8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNF8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF8 BINDING SITE, designated SEQ ID:10096, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30989] Another function of VGAM797 is therefore inhibition of Ring Finger Protein (C3HC4 type) 8 (RNF8, Accession NM\_003958). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNF8. LOC146894 (Accession NM\_145273) is another VGAM797 host target gene. LOC146894 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146894 BINDING SITE, designated SEQ ID:29782, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30990] Another function of VGAM797 is therefore inhibition of LOC146894 (Accession NM\_145273). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146894. LOC168391 (Accession XM\_095061) is another VGAM797 host target gene. LOC168391 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC168391, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC168391 BINDING SITE, designated SEQ ID:40244, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30991] Another function of VGAM797 is therefore inhibition of LOC168391 (Accession XM\_095061). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC168391. LOC255328 (Accession XM\_172920) is another VGAM797 host target gene. LOC255328 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255328, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255328 BINDING SITE, designated SEQ ID:46179, to the nucleotide sequence of VGAM797 RNA, herein designated VGAM RNA, also designated SEQ ID:3508.

[30992] Another function of VGAM797 is therefore inhibition of LOC255328 (Accession XM\_172920). Accordingly, utilities of VGAM797 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255328. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 798 (VGAM798) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[30993] VGAM798 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM798 was detected is described hereinabove with reference to Figs. 1–8.

[30994] VGAM798 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM798 host

target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[30995] VGAM798 gene encodes a VGAM798 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM798 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM798 precursor RNA is designated SEQ ID:784, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:784 is located at position 102198 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[30996] VGAM798 precursor RNA folds onto itself, forming VGAM798 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[30997] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM798 folded precursor RNA into VGAM798 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM798 RNA is designated SEQ ID:3509, and is provided hereinbelow with reference to the sequence listing part.

[30998] VGAM798 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM798 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM798 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[30999] VGAM798 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM798 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM798 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM798 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM798 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31000] The complementary binding of VGAM798 RNA, herein designated VGAM RNA, to host target binding sites on VGAM798 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM798 host target RNA into VGAM798 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31001] It is appreciated that VGAM798 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM798 host target genes. The mRNA of each one of this plurality of VGAM798 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM798 RNA, herein designated VGAM RNA, and which when bound by VGAM798 RNA causes inhibition of translation of respective one or more VGAM798 host target proteins.

[31002] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM798 gene, herein designated VGAM GENE, on one or more VGAM798 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are



also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31003] It is yet further appreciated that a function of VGAM798 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM798 correlate with, and may be deduced from, the identity of the host target genes which VGAM798 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31004] Nucleotide sequences of the VGAM798 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM798 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM798 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM798 are further

described hereinbelow with reference to Table 1.

[31005] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM798 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM798 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31006] As mentioned hereinabove with reference to Fig. 1, a function of VGAM798 gene, herein designated VGAM is inhibition of expression of VGAM798 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM798 correlate with, and may be deduced from, the identity of the target genes which VGAM798 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31007] Cysteine and Glycine-rich Protein 1 (CSRP1, Accession NM\_004078) is a VGAM798 host target gene. CSRP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSRP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of CSRP1 BINDING SITE, designated SEQ ID:10280, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31008] A function of VGAM798 is therefore inhibition of Cysteine and Glycine-rich Protein 1 (CSRP1, Accession NM\_004078), a gene which could play a role in neuronal development. Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSRP1. The function of CSRP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM743. Cullin 5 (CUL5, Accession NM\_003478) is another VGAM798 host target gene. CUL5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CUL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CUL5 BINDING SITE, designated SEQ ID:9548, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31009] Another function of VGAM798 is therefore inhibition of

Cullin 5 (CUL5, Accession NM\_003478), a gene which may target other proteins for ubiquitin-dependent proteolysis. Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CUL5. The function of CUL5 has been established by previous studies. The arginine vasopressin (AVP)-activated calcium-mobilizing receptor (OMIM Ref. No. VACM-1) is a cell surface protein involved in intracellular signal transduction. The gene encoding rabbit VACM-1 was isolated by Burnatowska-Hledin et al. (1995) from a renal medullary cDNA library by expression cloning in *Xenopus laevis* oocytes. While searching for expressed genes in the ataxia-telangiectasia (OMIM Ref. No. 208900) gene region on chromosome 11q22-q23, Byrd et al. (1997) identified the gene encoding the human homolog of rabbit VACM-1 and determined the complete amino acid sequence for the protein. The 780-amino acid predicted polypeptide differs from the rabbit sequence by only 7 residues. Northern hybridization analysis showed expression in a wide range of human tissues. Byrd et al. (1997) noted that the human VACM1 gene shares homology with the *C. elegans* gene *Ce-cul-5*, a member of the family of cullin genes that are involved in cell cycle regu-

lation.

- [31010] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [31011] Burnatowska-Hledin, M. A.; Spielman, W. S.; Smith, W. L.; Shi, P.; Meyer, J. M.; Dewitt, D. L. : Expression cloning of an AVP-activated, calcium-mobilizing receptor from rabbit kidney medulla. *Am. J. Physiol.* 268: F1198–F1210, 1995. ; and
- [31012] Byrd, P. J.; Stankovic, T.; McConville, C. M.; Smith, A. D.; Cooper, P. R.; Taylor, A. M. R. : Identification and analysis of expression of human VACM-1, a cullin gene family member loc.
- [31013] Further studies establishing the function and utilities of CUL5 are found in John Hopkins OMIM database record ID 601741, and in cited publications numbered 6200–6201 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cytochrome P450, Subfamily IVA, Polypeptide 11 (CYP4A11, Accession NM\_000778) is another VGAM798 host target gene. CYP4A11 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CYP4A11, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP4A11 BINDING SITE, designated SEQ ID:6420, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31014] Another function of VGAM798 is therefore inhibition of Cytochrome P450, Subfamily IVA, Polypeptide 11 (CYP4A11, Accession NM\_000778), a gene which catalyzes the omega- and (omega-1)-hydroxylation of various fatty acids . Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP4A11. The function of CYP4A11 has been established by previous studies. The human P450 enzymes encoded by CYP4 genes (see OMIM Ref. No. 124075) represent a distinct lineage of the P450 family. Palmer et al. (1993) noted that mammalian CYP4A enzymes catalyze selective hydroxylation of a primary carbon-hydrogen bond in medium- and long-chain fatty acids. Palmer et al. (1993) cloned and characterized a CYP4A-encoding gene (designated CYP4AII by them) by screening a human kidney cDNA library using a rabbit CYP4A cDNA probe. By Northern and RNase protection

analysis, they showed that the gene (also symbolized CYP4A11) is expressed predominantly in kidney and somewhat in liver. Palmer et al. (1993) characterized the catalytic activity of expressed recombinant CYP4A11 on various fatty acids and prostaglandins and concluded that the enzyme is a fatty acid omega-hydroxylase with turnover numbers of 9.8, 2.2, and 0.55 per min for lauric, palmitic, and arachidonic acids, respectively Imaoka et al. (1993) cloned a variant cDNA of CYP4A11, called CYP4A11v, from a human kidney cDNA library. The CYP4A11v cDNA contains a deletion of a single adenine residue, resulting in a frameshift and the production of a predicted 591-amino acid protein. Several differences in the 3-prime untranslated region of the CYP4A11v cDNA were also detected. Baculovirus-mediated expression of the CYP4A11v cDNA yielded an unstable protein that did not efficiently metabolize lauric acid.

[31015] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31016] Imaoka, S.; Ogawa, H.; Kimura, S.; Gonzalez, F. J. : Complete cDNA sequence and cDNA-directed expression of CYP4A11, a fatty acid omega-hydroxylase expressed in

human kidney. DNA Cell Biol. 12: 893–899, 1993. ; and

[31017] Kawashima, H.; Kusunose, E.; Kikuta, Y.; Kinoshita, H.; Tanaka, S.; Yamamoto, S.; Kishimoto, T.; Kusunose, M. : Purification and cDNA cloning of human liver CYP4A fatty acid omega-hydro.

[31018] Further studies establishing the function and utilities of CYP4A11 are found in John Hopkins OMIM database record ID 601310, and in cited publications numbered 7041–7044 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Glutamate Dehydrogenase 1 (GLUD1, Accession NM\_005271) is another VGAM798 host target gene. GLUD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GLUD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GLUD1 BINDING SITE, designated SEQ ID:11776, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31019] Another function of VGAM798 is therefore inhibition of Glutamate Dehydrogenase 1 (GLUD1, Accession



NM\_005271). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GLUD1. Roundabout, Axon Guidance Receptor, Homolog 1 (Drosophila) (ROBO1, Accession NM\_133631) is another VGAM798 host target gene. ROBO1 BINDING SITE1 and ROBO1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ROBO1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ROBO1 BINDING SITE1 and ROBO1 BINDING SITE2, designated SEQ ID:28590 and SEQ ID:8853 respectively, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31020] Another function of VGAM798 is therefore inhibition of Roundabout, Axon Guidance Receptor, Homolog 1 (Drosophila) (ROBO1, Accession NM\_133631), a gene which is an axon guidance receptor. Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ROBO1. The function of ROBO1 and its association with various diseases and clinical conditions, has been established by

previous studies, as described hereinabove with reference to VGAM37.Solute Carrier Family 18 (vesicular monoamine), Member 1 (SLC18A1, Accession NM\_003053) is another VGAM798 host target gene. SLC18A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC18A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC18A1 BINDING SITE, designated SEQ ID:9018, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31021] Another function of VGAM798 is therefore inhibition of Solute Carrier Family 18 (vesicular monoamine), Member 1 (SLC18A1, Accession NM\_003053), a gene which is involved in the vesicular transport of biogenic amines. Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC18A1. The function of SLC18A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM18.FLJ11539

(Accession NM\_024748) is another VGAM798 host target gene. FLJ11539 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11539, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11539 BINDING SITE, designated SEQ ID:24090, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31022] Another function of VGAM798 is therefore inhibition of FLJ11539 (Accession NM\_024748). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11539. FLJ14326 (Accession NM\_032191) is another VGAM798 host target gene. FLJ14326 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14326, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14326 BINDING SITE, designated SEQ ID:25906, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3509.

[31023] Another function of VGAM798 is therefore inhibition of FLJ14326 (Accession NM\_032191). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14326. KIAA0057 (Accession NM\_012288) is another VGAM798 host target gene. KIAA0057 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0057, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0057 BINDING SITE, designated SEQ ID:14628, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31024] Another function of VGAM798 is therefore inhibition of KIAA0057 (Accession NM\_012288). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0057. KIAA0961 (Accession NM\_014898) is another VGAM798 host target gene. KIAA0961 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0961, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0961 BINDING SITE, designated SEQ ID:17073, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31025] Another function of VGAM798 is therefore inhibition of KIAA0961 (Accession NM\_014898). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0961. LHX6 (Accession NM\_014368) is another VGAM798 host target gene. LHX6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LHX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LHX6 BINDING SITE, designated SEQ ID:15700, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31026] Another function of VGAM798 is therefore inhibition of LHX6 (Accession NM\_014368). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with LHX6.

MGC5139 (Accession XM\_058587) is another VGAM798 host target gene. MGC5139 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC5139, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5139 BINDING SITE, designated SEQ ID:36680, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31027] Another function of VGAM798 is therefore inhibition of MGC5139 (Accession XM\_058587). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5139. PFTAIRE Protein Kinase 1 (PFTK1, Accession NM\_012395) is another VGAM798 host target gene. PFTK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PFTK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PFTK1 BINDING SITE, designated SEQ ID:14756, to the

nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31028] Another function of VGAM798 is therefore inhibition of PFTAIK Protein Kinase 1 (PFTK1, Accession NM\_012395). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PFTK1. LOC133418 (Accession XM\_059649) is another VGAM798 host target gene. LOC133418 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133418, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133418 BINDING SITE, designated SEQ ID:37043, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31029] Another function of VGAM798 is therefore inhibition of LOC133418 (Accession XM\_059649). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133418. LOC51696 (Accession NM\_016217) is another VGAM798 host target gene. LOC51696 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51696 BINDING SITE, designated SEQ ID:18317, to the nucleotide sequence of VGAM798 RNA, herein designated VGAM RNA, also designated SEQ ID:3509.

[31030] Another function of VGAM798 is therefore inhibition of LOC51696 (Accession NM\_016217). Accordingly, utilities of VGAM798 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51696. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 799 (VGAM799) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31031] VGAM799 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM799 was detected is described hereinabove with reference to Figs. 1-8.



[31032] VGAM799 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM799 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31033] VGAM799 gene encodes a VGAM799 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM799 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM799 precursor RNA is designated SEQ ID:785, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:785 is located at position 181145 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[31034] VGAM799 precursor RNA folds onto itself, forming VGAM799 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31035] An enzyme complex designated DICER COMPLEX, `dices` the VGAM799 folded precursor RNA into VGAM799 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM799 RNA is designated SEQ ID:3510, and is provided hereinbelow with reference to the sequence listing part.

[31036] VGAM799 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM799 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM799 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31037] VGAM799 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM799 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM799 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM799 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM799 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31038] The complementary binding of VGAM799 RNA, herein designated VGAM RNA, to host target binding sites on VGAM799 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM799 host target RNA into VGAM799 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31039] It is appreciated that VGAM799 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM799 host target genes. The mRNA of each one of this plurality of VGAM799 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM799 RNA, herein designated VGAM RNA, and which when bound by VGAM799 RNA causes inhibition of translation of respective one or more VGAM799 host target proteins.

[31040] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM799 gene, herein designated VGAM GENE, on one or more VGAM799 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31041] It is yet further appreciated that a function of VGAM799 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM799 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM799 correlate with, and may be deduced from, the identity of the host target genes which VGAM799 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31042] Nucleotide sequences of the VGAM799 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM799 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM799 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM799 are further described hereinbelow with reference to Table 1.

[31043] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM799 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM799 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31044] As mentioned hereinabove with reference to Fig. 1, a function of VGAM799 gene, herein designated VGAM is inhibition of expression of VGAM799 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM799 correlate with, and may be deduced from, the identity of the target genes which VGAM799 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31045] Ankyrin 1, Erythrocytic (ANK1, Accession NM\_000037) is a VGAM799 host target gene. ANK1 BINDING SITE1 through ANK1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ANK1,

corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANK1 BINDING SITE1 through ANK1 BINDING SITE3, designated SEQ ID:5474, SEQ ID:21727 and SEQ ID:30277 respectively, to the nucleotide sequence of VGAM799 RNA, herein designated VGAM RNA, also designated SEQ ID:3510.

[31046] A function of VGAM799 is therefore inhibition of Ankyrin 1, Erythrocytic (ANK1, Accession NM\_000037). Accordingly, utilities of VGAM799 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANK1. KIAA1796 (Accession XM\_166146) is another VGAM799 host target gene. KIAA1796 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1796, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1796 BINDING SITE, designated SEQ ID:43962, to the nucleotide sequence of VGAM799 RNA, herein designated VGAM RNA, also designated SEQ ID:3510.

[31047] Another function of VGAM799 is therefore inhibition of

KIAA1796 (Accession XM\_166146). Accordingly, utilities of VGAM799 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1796. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 800 (VGAM800) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31048] VGAM800 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM800 was detected is described hereinabove with reference to Figs. 1–8.

[31049] VGAM800 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM800 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31050] VGAM800 gene encodes a VGAM800 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM800 precursor RNA does not encode a protein. A nucleotide



sequence identical or highly similar to the nucleotide sequence of VGAM800 precursor RNA is designated SEQ ID:786, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:786 is located at position 181601 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[31051] VGAM800 precursor RNA folds onto itself, forming VGAM800 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31052] An enzyme complex designated DICER COMPLEX, `dices` the VGAM800 folded precursor RNA into VGAM800 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 74%) nucleotide sequence of VGAM800 RNA is designated SEQ ID:3511, and is provided hereinbelow with reference to the sequence listing part.

[31053] VGAM800 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM800 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM800 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[31054] VGAM800 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM800 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM800 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM800 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM800 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31055] The complementary binding of VGAM800 RNA, herein designated VGAM RNA, to host target binding sites on VGAM800 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM800 host target RNA into VGAM800 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31056] It is appreciated that VGAM800 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM800 host target genes. The mRNA of each one of this plurality of VGAM800 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM800 RNA, herein designated VGAM RNA, and which when bound by VGAM800 RNA causes inhibition of translation of respective one or more VGAM800 host target proteins.

[31057] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM800 gene, herein designated VGAM GENE, on one or more VGAM800 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31058] It is yet further appreciated that a function of VGAM800 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM800 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM800 correlate with, and may be deduced from, the identity of the host target genes which VGAM800 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31059] Nucleotide sequences of the VGAM800 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM800 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM800 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM800 are further described hereinbelow with reference to Table 1.

[31060] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM800 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM800 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[31061] As mentioned hereinabove with reference to Fig. 1, a function of VGAM800 gene, herein designated VGAM is inhibition of expression of VGAM800 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM800 correlate with, and may be deduced from, the identity of the target genes which VGAM800 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31062] Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665) is a VGAM800 host target gene. EVI5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EVI5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVI5 BINDING SITE, designated SEQ ID:12216, to the nucleotide sequence of VGAM800 RNA, herein designated VGAM RNA, also designated SEQ ID:3511.

[31063] A function of VGAM800 is therefore inhibition of Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665). Accordingly, utilities of VGAM800 include diagnosis, preven-

tion and treatment of diseases and clinical conditions associated with EVI5. KIAA1789 (Accession XM\_040486) is another VGAM800 host target gene. KIAA1789 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1789, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1789 BINDING SITE, designated SEQ ID:33314, to the nucleotide sequence of VGAM800 RNA, herein designated VGAM RNA, also designated SEQ ID:3511.

[31064] Another function of VGAM800 is therefore inhibition of KIAA1789 (Accession XM\_040486). Accordingly, utilities of VGAM800 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1789. LOC221773 (Accession XM\_165802) is another VGAM800 host target gene. LOC221773 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221773, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221773 BINDING SITE, designated SEQ ID:43763, to

the nucleotide sequence of VGAM800 RNA, herein designated VGAM RNA, also designated SEQ ID:3511.

[31065] Another function of VGAM800 is therefore inhibition of LOC221773 (Accession XM\_165802). Accordingly, utilities of VGAM800 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221773. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 801 (VGAM801) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31066] VGAM801 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM801 was detected is described hereinabove with reference to Figs. 1–8.

[31067] VGAM801 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM801 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31068] VGAM801 gene encodes a VGAM801 precursor RNA,



herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM801 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM801 precursor RNA is designated SEQ ID:787, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:787 is located at position 962 relative to the genome of Murid Herpesvirus 4.

[31069] VGAM801 precursor RNA folds onto itself, forming VGAM801 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31070] An enzyme complex designated DICER COMPLEX, `dices` the VGAM801 folded precursor RNA into VGAM801 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 55%) nucleotide sequence of VGAM801 RNA is designated SEQ ID:3512, and is provided hereinbelow with reference to the sequence listing part.

[31071] VGAM801 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM801 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM801 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[31072] VGAM801 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM801 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM801 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM801 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM801 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31073] The complementary binding of VGAM801 RNA, herein designated VGAM RNA, to host target binding sites on VGAM801 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM801 host target RNA into VGAM801 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31074] It is appreciated that VGAM801 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM801 host target genes. The mRNA of each one of this plurality of VGAM801 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM801 RNA, herein designated VGAM RNA, and which when bound by VGAM801 RNA causes inhibition of translation of respective one or more VGAM801 host target proteins.

[31075] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM801 gene, herein designated VGAM GENE, on one or more VGAM801 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[31076] It is yet further appreciated that a function of VGAM801 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM801 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM801 correlate with, and may be deduced from, the identity of the host target genes which VGAM801 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31077] Nucleotide sequences of the VGAM801 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM801 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM801 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM801 are further described hereinbelow with reference to Table 1.

[31078] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM801 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM801 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31079] As mentioned hereinabove with reference to Fig. 1, a function of VGAM801 gene, herein designated VGAM is inhibition of expression of VGAM801 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM801 correlate with, and may be deduced from, the identity of the target genes which VGAM801 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31080] ATP10C (Accession NM\_024490) is a VGAM801 host target gene. ATP10C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP10C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP10C BINDING SITE, designated SEQ ID:23685, to the nucleotide sequence of VGAM801 RNA, herein designated VGAM RNA, also designated SEQ ID:3512.

[31081] A function of VGAM801 is therefore inhibition of ATP10C (Accession NM\_024490), a gene which is phosphorylated

in their intermediate state, drives uphill transport of ions across membranes. Accordingly, utilities of VGAM801 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP10C. The function of ATP10C has been established by previous studies. Meguro et al. (2001) reported that the ATP10C gene is maternally expressed, that it maps within the most common interval of deletion responsible for Angelman syndrome (AS; 105830) (15q11–q13), and that ATP10C expression is virtually absent from Angelman syndrome patients with imprinting mutations, as well as from patients with maternal deletions of 15q11–q13. Previously, although AS patients infrequently have mutations in the UBE3A gene (OMIM Ref. No. 601623), which encodes a ubiquitin ligase required for long-term synaptic potentiation (LTP), most cases were attributable to de novo maternal deletions of the critical 15q region. Herzing et al. (2001) reported that ATP10C maps within 200 kb distal to UBE3A and, like UBE3A, demonstrates imprinted, preferential maternal expression in human brain. They suggested that ATP10C is a candidate for chromosome 15-associated autism as well as the Angelman syndrome phenotype. Animal model experiments lend further support to the function of ATP10C.

Dhar et al. (2000) reported that maternal inheritance of deletions of the mouse Atp10c gene resulted in increased body fat. The obese phenotype was consistently observed in the mouse model for Angelman syndrome with paternal uniparental disomy (Cattanach et al., 1997). Meguro et al. (2001) speculated that ATP10C may be an aminophospholipid translocase involved in phospholipid transport.

[31082] It is appreciated that the abovementioned animal model for ATP10C is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[31083] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31084] Meguro, M.; Kashiwagi, A.; Mitsuya, K.; Nakao, M.; Kondo, I.; Saitoh, S.; Oshimura, M. : A novel maternally expressed gene, ATP10C, encodes a putative aminophospholipid translocase associated with Angelman syndrome. *Nature Genet.* 28: 19–20, 2001. ; and

[31085] Cattanach, B. M.; Barr, J. A.; Beechey, C. V.; Martin, J.; Noebels, J.; Jones, J. : A candidate model for Angelman syndrome in the mouse. *Mammalian Genome* 8: 472–478, 1997.



[31086] Further studies establishing the function and utilities of ATP10C are found in John Hopkins OMIM database record ID 605855, and in cited publications numbered 6621–6622, 12269, 676 and 6779 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Meningioma Expressed Antigen 5 (hyaluronidase) (MGEA5, Accession NM\_012215) is another VGAM801 host target gene. MGEA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGEA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGEA5 BINDING SITE, designated SEQ ID:14516, to the nucleotide sequence of VGAM801 RNA, herein designated VGAM RNA, also designated SEQ ID:3512.

[31087] Another function of VGAM801 is therefore inhibition of Meningioma Expressed Antigen 5 (hyaluronidase) (MGEA5, Accession NM\_012215), a gene which has a hyaluronidase activity. Accordingly, utilities of VGAM801 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGEA5. The function of MGEA5 has been established by previous studies. By screening a

meningioma expression library with autologous serum, Heckel et al. (1998) identified 4 cDNA clones representing a novel gene, which they designated meningioma-expressed antigen-5, with striking homology to *C. elegans* hyaluronidase. MGEA5 was noted to have hyaluronidase activity, but was otherwise not characterized. By sequencing randomly selected cDNAs corresponding to relatively long transcripts from human brain, Ishikawa et al. (1998) isolated an MGEA5 cDNA, which they designated KIAA0679, encoding a deduced 767-amino acid protein.

[31088] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31089] Heckel, D.; Comtesse, N.; Brass, N.; Blin, N.; Zang, K. D.; Meese, E. : Novel immunogenic antigen homologous to hyaluronidase in meningioma. *Hum. Molec. Genet.* 7: 1859-1872, 1998. ; and

[31090] Ishikawa, K.; Nagase, T.; Suyama, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. X. The complete sequences.

[31091] Further studies establishing the function and utilities of MGEA5 are found in John Hopkins OMIM database record

ID 604039, and in cited publications numbered 820 and 9440 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. MSTP032 (Accession NM\_025226) is another VGAM801 host target gene. MSTP032 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSTP032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSTP032 BINDING SITE, designated SEQ ID:24903, to the nucleotide sequence of VGAM801 RNA, herein designated VGAM RNA, also designated SEQ ID:3512.

[31092] Another function of VGAM801 is therefore inhibition of MSTP032 (Accession NM\_025226). Accordingly, utilities of VGAM801 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSTP032. TED (Accession NM\_015686) is another VGAM801 host target gene. TED BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TED, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of TED BINDING SITE, designated SEQ ID:17910, to the nucleotide sequence of VGAM801 RNA, herein designated VGAM RNA, also designated SEQ ID:3512.

[31093] Another function of VGAM801 is therefore inhibition of TED (Accession NM\_015686). Accordingly, utilities of VGAM801 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TED. LOC151126 (Accession XM\_087103) is another VGAM801 host target gene. LOC151126 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151126, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151126 BINDING SITE, designated SEQ ID:39055, to the nucleotide sequence of VGAM801 RNA, herein designated VGAM RNA, also designated SEQ ID:3512.

[31094] Another function of VGAM801 is therefore inhibition of LOC151126 (Accession XM\_087103). Accordingly, utilities of VGAM801 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151126. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 802 (VGAM802) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31095] VGAM802 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM802 was detected is described hereinabove with reference to Figs. 1–8.

[31096] VGAM802 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM802 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31097] VGAM802 gene encodes a VGAM802 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM802 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM802 precursor RNA is designated SEQ ID:788, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:788 is

located at position 638 relative to the genome of Murid Herpesvirus 4.

[31098] VGAM802 precursor RNA folds onto itself, forming VGAM802 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31099] An enzyme complex designated DICER COMPLEX, `dices` the VGAM802 folded precursor RNA into VGAM802 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 88%) nucleotide sequence of VGAM802 RNA is designated SEQ ID:3513, and is provided hereinbelow with reference to the sequence listing part.

[31100] VGAM802 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM802 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM802 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[31101] VGAM802 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM802 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM802 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM802 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM802 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31102] The complementary binding of VGAM802 RNA, herein designated VGAM RNA, to host target binding sites on VGAM802 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM802 host target RNA into VGAM802 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31103] It is appreciated that VGAM802 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM802 host target genes. The mRNA of each one of this plurality of VGAM802 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM802 RNA, herein designated VGAM RNA, and which when bound by VGAM802 RNA causes inhibition of translation of respective one or more VGAM802



host target proteins.

[31104] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM802 gene, herein designated VGAM GENE, on one or more VGAM802 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31105] It is yet further appreciated that a function of VGAM802 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Spe-

cific functions, and accordingly utilities, of VGAM802 correlate with, and may be deduced from, the identity of the host target genes which VGAM802 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31106] Nucleotide sequences of the VGAM802 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM802 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM802 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM802 are further described hereinbelow with reference to Table 1.

[31107] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM802 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM802 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31108] As mentioned hereinabove with reference to Fig. 1, a function of VGAM802 gene, herein designated VGAM is inhibition of expression of VGAM802 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM802 correlate with, and may be deduced from, the identity of the target genes which VGAM802 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31109] Cholinergic Receptor, Nicotinic, Beta Polypeptide 2 (neuronal) (CHRNA2, Accession NM\_000748) is a VGAM802 host target gene. CHRNA2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CHRNA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHRNA2 BINDING SITE, designated SEQ ID:6402, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31110] A function of VGAM802 is therefore inhibition of Cholinergic Receptor, Nicotinic, Beta Polypeptide 2 (neuronal) (CHRNA2, Accession NM\_000748), a gene which mediates fast signal transmission at synapses. Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHRNA2. The function of CHRNA2 and its association with various diseases and clinical conditions, has been estab-

lished by previous studies, as described hereinabove with reference to VGAM166. Myeloid/lymphoid Or Mixed-lineage Leukemia (trithorax homolog, Drosophila); Translocated To, 2 (MLLT2, Accession NM\_005935) is another VGAM802 host target gene. MLLT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MLLT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MLLT2 BINDING SITE, designated SEQ ID:12569, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31111] Another function of VGAM802 is therefore inhibition of Myeloid/lymphoid Or Mixed-lineage Leukemia (trithorax homolog, Drosophila); Translocated To, 2 (MLLT2, Accession NM\_005935), a gene which is a Putative transcription factor. Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MLLT2. The function of MLLT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM57. Thyroid

Hormone Receptor, Beta (erythroblastic leukemia viral (v-erb-a) Oncogene Homolog 2, Avian) (THRB, Accession NM\_000461) is another VGAM802 host target gene. THRB BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by THRB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of THRB BINDING SITE, designated SEQ ID:6076, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31112] Another function of VGAM802 is therefore inhibition of Thyroid Hormone Receptor, Beta (erythroblastic leukemia viral (v-erb-a) Oncogene Homolog 2, Avian) (THRB, Accession NM\_000461). Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with THRB. FLJ11413 (Accession NM\_024554) is another VGAM802 host target gene. FLJ11413 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ11413, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of FLJ11413 BINDING SITE, designated SEQ ID:23774, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31113] Another function of VGAM802 is therefore inhibition of FLJ11413 (Accession NM\_024554). Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11413. Interleukin 14 (IL14, Accession XM\_170924) is another VGAM802 host target gene. IL14 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by IL14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL14 BINDING SITE, designated SEQ ID:45702, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31114] Another function of VGAM802 is therefore inhibition of Interleukin 14 (IL14, Accession XM\_170924). Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL14. KIAA0916 (Accession NM\_015057) is another

VGAM802 host target gene. KIAA0916 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0916, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0916 BINDING SITE, designated SEQ ID:17416, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31115] Another function of VGAM802 is therefore inhibition of KIAA0916 (Accession NM\_015057). Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0916. KRT6IRS (Accession NM\_033448) is another VGAM802 host target gene. KRT6IRS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KRT6IRS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KRT6IRS BINDING SITE, designated SEQ ID:27252, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31116] Another function of VGAM802 is therefore inhibition of KRT6IRS (Accession NM\_033448). Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KRT6IRS. LOC137991 (Accession XM\_059934) is another VGAM802 host target gene. LOC137991 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC137991, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC137991 BINDING SITE, designated SEQ ID:37114, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31117] Another function of VGAM802 is therefore inhibition of LOC137991 (Accession XM\_059934). Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC137991. LOC151234 (Accession XM\_087136) is another VGAM802 host target gene. LOC151234 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151234, corresponding to a HOST TARGET binding site such as BIND-



ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151234 BINDING SITE, designated SEQ ID:39077, to the nucleotide sequence of VGAM802 RNA, herein designated VGAM RNA, also designated SEQ ID:3513.

[31118] Another function of VGAM802 is therefore inhibition of LOC151234 (Accession XM\_087136). Accordingly, utilities of VGAM802 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151234. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 803 (VGAM803) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31119] VGAM803 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM803 was detected is described hereinabove with reference to Figs. 1–8.

[31120] VGAM803 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM803 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[31121] VGAM803 gene encodes a VGAM803 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM803 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM803 precursor RNA is designated SEQ ID:789, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:789 is located at position 201 relative to the genome of Murid Herpesvirus 4.

[31122] VGAM803 precursor RNA folds onto itself, forming VGAM803 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31123] An enzyme complex designated DICER COMPLEX, `dices` the VGAM803 folded precursor RNA into VGAM803 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM803 RNA is designated SEQ ID:3514, and is provided hereinbelow with reference to the sequence listing part.

[31124] VGAM803 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM803 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM803 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31125] VGAM803 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM803 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM803 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM803 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM803 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31126] The complementary binding of VGAM803 RNA, herein designated VGAM RNA, to host target binding sites on VGAM803 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM803 host target RNA into VGAM803 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[31127] It is appreciated that VGAM803 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM803 host target genes. The mRNA of each one of this plurality of VGAM803 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM803 RNA, herein designated VGAM RNA, and which when bound by VGAM803 RNA causes inhibition of translation of respective one or more VGAM803 host target proteins.

[31128] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM803 gene, herein designated VGAM GENE, on one or more VGAM803 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31129] It is yet further appreciated that a function of VGAM803 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM803 correlate with, and may be deduced from, the identity of the host target genes which VGAM803 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31130] Nucleotide sequences of the VGAM803 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM803 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM803 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM803 are further described hereinbelow with reference to Table 1.

[31131] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM803 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM803 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31132] As mentioned hereinabove with reference to Fig. 1, a function of VGAM803 gene, herein designated VGAM is inhibition of expression of VGAM803 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM803 correlate with, and may be deduced from, the identity of the target genes which VGAM803 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31133] Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104) is a VGAM803 host target gene. BACE BINDING SITE1 and BACE BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by BACE, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BACE BINDING SITE1 and BACE BINDING SITE2, designated SEQ ID:14416 and SEQ

ID:29084 respectively, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31134] A function of VGAM803 is therefore inhibition of Beta-site APP-cleaving Enzyme (BACE, Accession NM\_012104), a gene which is responsible for the proteolytic processing of the amyloid precursor protein. Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BACE. The function of BACE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM173. Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437) is another VGAM803 host target gene. NCOA4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCOA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA4 BINDING SITE, designated SEQ ID:11924, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.



[31135] Another function of VGAM803 is therefore inhibition of Nuclear Receptor Coactivator 4 (NCOA4, Accession NM\_005437), a gene which Binds and activates androgen receptor (AR) in ligand-dependent manner. Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA4. The function of NCOA4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM420. Phosphoinositide-3-kinase, Class 2, Beta Polypeptide (PIK3C2B, Accession NM\_002646) is another VGAM803 host target gene. PIK3C2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIK3C2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIK3C2B BINDING SITE, designated SEQ ID:8507, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31136] Another function of VGAM803 is therefore inhibition of Phosphoinositide-3-kinase, Class 2, Beta Polypeptide

(PIK3C2B, Accession NM\_002646). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIK3C2B. Surfactant, Pulmonary-associated Protein A2 (SFTPA2, Accession NM\_006926) is another VGAM803 host target gene. SFTPA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFTPA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFTPA2 BINDING SITE, designated SEQ ID:13807, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31137] Another function of VGAM803 is therefore inhibition of Surfactant, Pulmonary-associated Protein A2 (SFTPA2, Accession NM\_006926), a gene which plays a role in innate host defense in the lung. Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFTPA2. The function of SFTPA2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference

to VGAM148. Small Nuclear Ribonucleoprotein 70kDa Polypeptide (RNP antigen) (SNRP70, Accession XM\_085942) is another VGAM803 host target gene. SNRP70 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SNRP70, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNRP70 BINDING SITE, designated SEQ ID:38406, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31138] Another function of VGAM803 is therefore inhibition of Small Nuclear Ribonucleoprotein 70kDa Polypeptide (RNP antigen) (SNRP70, Accession XM\_085942), a gene which mediates the splicing of pre-mRNA by binding to the loop I region of U1-snRNA. Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNRP70. The function of SNRP70 has been established by previous studies. The series of reactions leading to the removal of intervening sequences from pre-mRNAs to yield mature mRNA occurs in a complex known as the spliceosome. The

spliceosome contains several small nuclear ribonucleo-protein complexes (OMIM Ref. No. snRNPs). One of these, the U1 snRNP, contains at least 3 specific proteins. For the largest of these, the 68-kD U1-snRNP protein, a cDNA has been isolated. By use of the cDNA clone and the study of somatic cell hybrids, Barton et al. (1987) demonstrated that the gene encoding this protein is located on chromosome 19. See also Spritz et al. (1987, 1987). Spritz et al. (1987, 1987) referred to the protein as U1-70K snRNP protein. They suggested that the actual size is probably 52 kD. The protein contains 3 regions similar to known nucleic acid-binding proteins, and it binds RNA in an in vitro assay. Multiple forms due to alternative splicing may exist, possibly with different functions in vivo. The human U1-70K snRNP protein is the major antigen recognized by anti-(U1)RNP sera from patients with autoimmune diseases. Montzka and Steitz (1988) demonstrated additional complexity of the human snRNPs and stated that there are at least 12 snRNPs. Spritz et al. (1990) mapped the SNRP70 gene to 19q13.3 by a combination of Southern analysis of DNAs from somatic cell hybrids and in situ hybridization. They reported that the gene is greater than 44 kb, with 11 exons. Nelissen et al. (1991) likewise mapped

the gene to 19q and concluded that it is present in single copy, but stated that it consists of 6 exons and is 14 to 16 kb long.

[31139] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31140] Montzka, K. A.; Steitz, J. A. : Additional low-abundance human small nuclear ribonucleoproteins: U11, U12, etc. Proc. Nat. Acad. Sci. 85: 8885–8889, 1988. ; and

[31141] Nelissen, R. L.; Sillekens, P. T.; Beijer, R. P.; Geurts van Kessel, A. H.; van Venrooij, W. J. : Structure, chromosomal localization and evolutionary conservation of the gene encoding.

[31142] Further studies establishing the function and utilities of SNRP70 are found in John Hopkins OMIM database record ID 180740, and in cited publications numbered 746–75 and 1549 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Thromboxane A Synthase 1 (platelet, cytochrome P450, subfamily V) (TBXAS1, Accession NM\_030984) is another VGAM803 host target gene. TBXAS1 BINDING SITE1 and TBXAS1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded

by TBXAS1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBXAS1 BINDING SITE1 and TBXAS1 BINDING SITE2, designated SEQ ID:25246 and SEQ ID:6732 respectively, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31143] Another function of VGAM803 is therefore inhibition of Thromboxane A Synthase 1 (platelet, cytochrome P450, subfamily V) (TBXAS1, Accession NM\_030984). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TBXAS1. Chromatin Accessibility Complex 1 (CHRAC1, Accession NM\_017444) is another VGAM803 host target gene. CHRAC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CHRAC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHRAC1 BINDING SITE, designated SEQ ID:18905, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3514.

[31144] Another function of VGAM803 is therefore inhibition of Chromatin Accessibility Complex 1 (CHRAC1, Accession NM\_017444). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHRAC1. DKFZP586B2420 (Accession XM\_059482) is another VGAM803 host target gene. DKFZP586B2420 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP586B2420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586B2420 BINDING SITE, designated SEQ ID:37011, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31145] Another function of VGAM803 is therefore inhibition of DKFZP586B2420 (Accession XM\_059482). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586B2420. FLJ10044 (Accession NM\_017980) is another VGAM803 host target gene. FLJ10044 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by FLJ10044, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10044 BINDING SITE, designated SEQ ID:19711, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31146] Another function of VGAM803 is therefore inhibition of FLJ10044 (Accession NM\_017980). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10044. FLJ11320 (Accession NM\_018389) is another VGAM803 host target gene. FLJ11320 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11320, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11320 BINDING SITE, designated SEQ ID:20424, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31147] Another function of VGAM803 is therefore inhibition of FLJ11320 (Accession NM\_018389). Accordingly, utilities of



VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11320. FLJ21940 (Accession NM\_022828) is another VGAM803 host target gene. FLJ21940 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ21940, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21940 BINDING SITE, designated SEQ ID:23107, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31148] Another function of VGAM803 is therefore inhibition of FLJ21940 (Accession NM\_022828). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21940. FLJ23047 (Accession NM\_024548) is another VGAM803 host target gene. FLJ23047 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23047, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23047 BINDING SITE,

designated SEQ ID:23762, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31149] Another function of VGAM803 is therefore inhibition of FLJ23047 (Accession NM\_024548). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23047. FLJ23185 (Accession NM\_025056) is another VGAM803 host target gene. FLJ23185 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ23185, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23185 BINDING SITE, designated SEQ ID:24653, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31150] Another function of VGAM803 is therefore inhibition of FLJ23185 (Accession NM\_025056). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23185. FLJ23309 (Accession NM\_024896) is another VGAM803 host target gene. FLJ23309 BINDING SITE is HOST TARGET

binding site found in the 3` untranslated region of mRNA encoded by FLJ23309, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23309 BINDING SITE, designated SEQ ID:24378, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31151] Another function of VGAM803 is therefore inhibition of FLJ23309 (Accession NM\_024896). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23309. Phosphatidylinositol-4-phosphate 5-kinase, Type I, Gamma (PIP5K1C, Accession XM\_047620) is another VGAM803 host target gene. PIP5K1C BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PIP5K1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIP5K1C BINDING SITE, designated SEQ ID:35015, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31152] Another function of VGAM803 is therefore inhibition of Phosphatidylinositol-4-phosphate 5-kinase, Type I, Gamma (PIP5K1C, Accession XM\_047620). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP5K1C. LOC144558 (Accession XM\_096629) is another VGAM803 host target gene. LOC144558 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144558, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144558 BINDING SITE, designated SEQ ID:40437, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31153] Another function of VGAM803 is therefore inhibition of LOC144558 (Accession XM\_096629). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144558. LOC145371 (Accession XM\_085123) is another VGAM803 host target gene. LOC145371 BINDING SITE1 and LOC145371 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA en-

coded by LOC145371, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145371 BINDING SITE1 and LOC145371 BINDING SITE2, designated SEQ ID:37848 and SEQ ID:37847 respectively, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31154] Another function of VGAM803 is therefore inhibition of LOC145371 (Accession XM\_085123). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145371. LOC161742 (Accession XM\_091095) is another VGAM803 host target gene. LOC161742 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC161742, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161742 BINDING SITE, designated SEQ ID:40026, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31155] Another function of VGAM803 is therefore inhibition of

LOC161742 (Accession XM\_091095). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161742. LOC201191 (Accession XM\_117058) is another VGAM803 host target gene. LOC201191 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201191, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201191 BINDING SITE, designated SEQ ID:43213, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31156] Another function of VGAM803 is therefore inhibition of LOC201191 (Accession XM\_117058). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201191. LOC221486 (Accession XM\_165760) is another VGAM803 host target gene. LOC221486 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221486, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC221486 BINDING SITE, designated SEQ ID:43740, to the nucleotide sequence of VGAM803 RNA, herein designated VGAM RNA, also designated SEQ ID:3514.

[31157] Another function of VGAM803 is therefore inhibition of LOC221486 (Accession XM\_165760). Accordingly, utilities of VGAM803 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221486. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 804 (VGAM804) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31158] VGAM804 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM804 was detected is described hereinabove with reference to Figs. 1–8.

[31159] VGAM804 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM804 host target gene, herein designated VGAM HOST TARGET GENE,

is a human gene contained in the human genome.

[31160] VGAM804 gene encodes a VGAM804 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM804 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM804 precursor RNA is designated SEQ ID:790, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:790 is located at position 229000 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[31161] VGAM804 precursor RNA folds onto itself, forming VGAM804 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31162] An enzyme complex designated DICER COMPLEX, `dices` the VGAM804 folded precursor RNA into VGAM804 RNA,



herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM804 RNA is designated SEQ ID:3515, and is provided hereinbelow with reference to the sequence listing part.

[31163] VGAM804 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM804 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM804 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31164] VGAM804 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM804 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM804 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM804 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM804 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31165] The complementary binding of VGAM804 RNA, herein designated VGAM RNA, to host target binding sites on VGAM804 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM804 host target RNA into VGAM804 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[31166] It is appreciated that VGAM804 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM804 host target genes. The mRNA of each one of this plurality of VGAM804 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM804 RNA, herein designated VGAM RNA, and which when bound by VGAM804 RNA causes inhibition of translation of respective one or more VGAM804 host target proteins.

[31167] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM804 gene, herein designated VGAM GENE, on one or more VGAM804 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31168] It is yet further appreciated that a function of VGAM804 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM804 correlate with, and may be deduced from, the identity of the host target genes which VGAM804 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31169] Nucleotide sequences of the VGAM804 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM804 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM804 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM804 are further described hereinbelow with reference to Table 1.

- [31170] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM804 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM804 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [31171] As mentioned hereinabove with reference to Fig. 1, a function of VGAM804 gene, herein designated VGAM is inhibition of expression of VGAM804 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM804 correlate with, and may be deduced from, the identity of the target genes which VGAM804 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [31172] Caveolin 1, Caveolae Protein, 22kDa (CAV1, Accession NM\_001753) is a VGAM804 host target gene. CAV1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CAV1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAV1 BINDING SITE, designated SEQ ID:7492, to the nucleotide

sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31173] A function of VGAM804 is therefore inhibition of Caveolin 1, Caveolae Protein, 22kDa (CAV1, Accession NM\_001753), a gene which may act as a scaffolding protein within caveolar membranes, and interacts directly with g-protein alpha subunits and can functionally regulate their activity. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAV1. The function of CAV1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM331. CD53 Antigen (CD53, Accession NM\_000560) is another VGAM804 host target gene. CD53 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CD53, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD53 BINDING SITE, designated SEQ ID:6169, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31174] Another function of VGAM804 is therefore inhibition of CD53 Antigen (CD53, Accession NM\_000560). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD53. Cadherin, EGF LAG Seven-pass G-type Receptor 1 (flamingo homolog, Drosophila) (CELSR1, Accession NM\_014246) is another VGAM804 host target gene. CELSR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CELSR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CELSR1 BINDING SITE, designated SEQ ID:15514, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31175] Another function of VGAM804 is therefore inhibition of Cadherin, EGF LAG Seven-pass G-type Receptor 1 (flamingo homolog, Drosophila) (CELSR1, Accession NM\_014246), a gene which is involved in contact-mediated communication. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CELSR1. The func-

tion of CELSR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM459. Dual-specificity tyrosine-(Y)-phosphorylation Regulated Kinase 2 (DYRK2, Accession NM\_003583) is another VGAM804 host target gene. DYRK2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DYRK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DYRK2 BINDING SITE, designated SEQ ID:9634, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31176] Another function of VGAM804 is therefore inhibition of Dual-specificity tyrosine-(Y)-phosphorylation Regulated Kinase 2 (DYRK2, Accession NM\_003583). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DYRK2. Eve, Even-skipped Homeo Box Homolog 1 (Drosophila) (EVX1, Accession NM\_001989) is another VGAM804 host target gene. EVX1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region



of mRNA encoded by EVX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVX1 BINDING SITE, designated SEQ ID:7714, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31177] Another function of VGAM804 is therefore inhibition of Eve, Even-skipped Homeo Box Homolog 1 (Drosophila) (EVX1, Accession NM\_001989). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EVX1. Coagulation Factor II (thrombin) Receptor-like 3 (F2RL3, Accession NM\_003950) is another VGAM804 host target gene. F2RL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by F2RL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F2RL3 BINDING SITE, designated SEQ ID:10086, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31178] Another function of VGAM804 is therefore inhibition of Coagulation Factor II (thrombin) Receptor-like 3 (F2RL3, Accession NM\_003950), a gene which Protease-activated receptor 4; G protein-coupled receptor that increases phosphoinositide hydrolysis. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F2RL3. The function of F2RL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM193. Fibronectin Leucine Rich Transmembrane Protein 2 (FLRT2, Accession NM\_013231) is another VGAM804 host target gene. FLRT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLRT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLRT2 BINDING SITE, designated SEQ ID:14888, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31179] Another function of VGAM804 is therefore inhibition of Fibronectin Leucine Rich Transmembrane Protein 2 (FLRT2,

Accession NM\_013231), a gene which may have a function in cell adhesion and/or receptor signaling. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLRT2. The function of FLRT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. Membrane-spanning 4-domains, Subfamily A, Member 2 (Fc fragment of IgE, high affinity I, receptor for; beta polypeptide) (MS4A2, Accession NM\_021950) is another VGAM804 host target gene. MS4A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MS4A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MS4A2 BINDING SITE, designated SEQ ID:22478, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31180] Another function of VGAM804 is therefore inhibition of Membrane-spanning 4-domains, Subfamily A, Member 2 (Fc fragment of IgE, high affinity I, receptor for; beta

polypeptide) (MS4A2, Accession NM\_021950), a gene which binds to the fc region of immunoglobulins epsilon. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MS4A2. The function of MS4A2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM636. Myeloma Overexpressed Gene (in a subset of t(11;14) Positive Multiple Myelomas) (MYEOV, Accession NM\_138768) is another VGAM804 host target gene. MYEOV BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYEOV, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYEOV BINDING SITE, designated SEQ ID:29003, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31181] Another function of VGAM804 is therefore inhibition of Myeloma Overexpressed Gene (in a subset of t(11;14) Positive Multiple Myelomas) (MYEOV, Accession NM\_138768), a gene which is encoded by MYELOMA

OVEREXPRESSED GENE. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYEOV. The function of MYEOV and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM471. Nuclear Receptor Coactivator 6 (NCOA6, Accession NM\_014071) is another VGAM804 host target gene. NCOA6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NCOA6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA6 BINDING SITE, designated SEQ ID:15296, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31182] Another function of VGAM804 is therefore inhibition of Nuclear Receptor Coactivator 6 (NCOA6, Accession NM\_014071), a gene which activates gene transcription through ligand-dependent association with coactivators. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with NCOA6. The function of NCOA6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM25. Protein Kinase, CAMP-dependent, Catalytic, Alpha (PRKACA, Accession NM\_002730) is another VGAM804 host target gene. PRKACA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKACA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKACA BINDING SITE, designated SEQ ID:8600, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31183] Another function of VGAM804 is therefore inhibition of Protein Kinase, CAMP-dependent, Catalytic, Alpha (PRKACA, Accession NM\_002730), a gene which phosphorylates target proteins on serine or threonine residues. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKACA. The function of PRKACA and its association with various diseases and clinical conditions,

has been established by previous studies, as described hereinabove with reference to VGAM175.Arginine–glutamic Acid Dipeptide (RE) Repeats (RERE, Accession NM\_012102) is another VGAM804 host target gene. RERE BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RERE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RERE BINDING SITE, designated SEQ ID:14412, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31184] Another function of VGAM804 is therefore inhibition of Arginine–glutamic Acid Dipeptide (RE) Repeats (RERE, Accession NM\_012102), a gene which binds DRPLA and locates in the nucleus. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RERE. The function of RERE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM51.Selectin P Ligand (SELPLG, Accession XM\_006867) is another

VGAM804 host target gene. SELPLG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SELPLG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SELPLG BINDING SITE, designated SEQ ID:30018, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31185] Another function of VGAM804 is therefore inhibition of Selectin P Ligand (SELPLG, Accession XM\_006867), a gene which binds to p-, e- and l-selectins, which mediates the tethering and rolling of neutrophils and t-lymphocytes on endothelial cells. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SELPLG. The function of SELPLG and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200. Zinc Finger Protein 200 (ZNF200, Accession NM\_003454) is another VGAM804 host target gene. ZNF200 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF200, corresponding to a



HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF200 BINDING SITE, designated SEQ ID:9505, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31186] Another function of VGAM804 is therefore inhibition of Zinc Finger Protein 200 (ZNF200, Accession NM\_003454). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF200. Zinc Finger Protein 36 (KOX 18) (ZNF36, Accession XM\_168302) is another VGAM804 host target gene. ZNF36 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF36, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF36 BINDING SITE, designated SEQ ID:45103, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31187] Another function of VGAM804 is therefore inhibition of Zinc Finger Protein 36 (KOX 18) (ZNF36, Accession

XM\_168302), a gene which may be involved in transcriptional regulation. Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF36. The function of ZNF36 has been established by previous studies. By screening a human insulinoma cDNA library with a degenerate oligonucleotide corresponding to the H/C linker sequence, Tommerup et al. (1993) isolated cDNAs potentially encoding zinc finger proteins. Tommerup and Vissing (1995) performed sequence analysis on a number of these cDNAs and identified several novel zinc finger protein genes, including ZNF36, which they called ZNF139. The ZNF139 cDNA predicts a protein belonging to the Kruppel family of zinc finger proteins. By isotopic in situ hybridization, Rousseau-Merck et al. (1995) mapped the ZNF36 gene, which they called KOX18, to 7q21-q22. From pulsed field gel electrophoresis studies, they showed that KOX18 is within less than 250 kb of KOX25 (ZNF38; 601261). Rousseau-Merck et al. (1995) tabulated 18 different KOX genes that had been located in pairs within 9 DNA fragments of 200 to 580 kb on 7 different chromosomes. By FISH, Tommerup and Vissing (1995) mapped the ZNF36 gene to 7q21.3-q22.1.

[31188] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31189] Tommerup, N.; Vissing, H. : Isolation and fine mapping of 16 novel human zinc finger–encoding cDNAs identify putative candidate genes for developmental and malignant disorders. *Genomics* 27: 259–264, 1995. ; and

[31190] Rousseau–Merck, M.–F.; Duro, D.; Berger, R.; Thiesen, H. J. : Chromosomal localization of two KOX zinc finger genes on chromosome bands 7q21–q22. *Ann. Genet.* 38: 81–84, 1995.

[31191] Further studies establishing the function and utilities of ZNF36 are found in John Hopkins OMIM database record ID 601260, and in cited publications numbered 925 and 9255 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. AD034

(Accession NM\_031480) is another VGAM804 host target gene. AD034 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AD034, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AD034 BINDING SITE, designated SEQ

ID:25560, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31192] Another function of VGAM804 is therefore inhibition of AD034 (Accession NM\_031480). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AD034. Apolipoprotein L, 6 (APOL6, Accession NM\_030641) is another VGAM804 host target gene. APOL6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APOL6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APOL6 BINDING SITE, designated SEQ ID:24971, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31193] Another function of VGAM804 is therefore inhibition of Apolipoprotein L, 6 (APOL6, Accession NM\_030641). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APOL6. Rho GTPase Activating Protein 5 (ARHGAP5, Accession XM\_085082) is another VGAM804

host target gene. ARHGAP5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGAP5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP5 BINDING SITE, designated SEQ ID:37823, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31194] Another function of VGAM804 is therefore inhibition of Rho GTPase Activating Protein 5 (ARHGAP5, Accession XM\_085082). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP5. BCAA (Accession NM\_016374) is another VGAM804 host target gene. BCAA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BCAA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCAA BINDING SITE, designated SEQ ID:18510, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31195] Another function of VGAM804 is therefore inhibition of BCAA (Accession NM\_016374). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCAA. Chromosome 20 Open Reading Frame 13 (C20orf13, Accession NM\_017714) is another VGAM804 host target gene. C20orf13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf13 BINDING SITE, designated SEQ ID:19299, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31196] Another function of VGAM804 is therefore inhibition of Chromosome 20 Open Reading Frame 13 (C20orf13, Accession NM\_017714). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf13. C3F (Accession NM\_005768) is another VGAM804 host target gene. C3F BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

C3F, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C3F BINDING SITE, designated SEQ ID:12333, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31197] Another function of VGAM804 is therefore inhibition of C3F (Accession NM\_005768). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C3F. Cytoskeleton-associated Protein 4 (CKAP4, Accession NM\_006825) is another VGAM804 host target gene. CKAP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CKAP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CKAP4 BINDING SITE, designated SEQ ID:13704, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31198] Another function of VGAM804 is therefore inhibition of Cytoskeleton-associated Protein 4 (CKAP4, Accession

NM\_006825). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CKAP4. CRIPT (Accession XM\_057669) is another VGAM804 host target gene. CRIPT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRIPT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRIPT BINDING SITE, designated SEQ ID:36540, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31199] Another function of VGAM804 is therefore inhibition of CRIPT (Accession XM\_057669). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRIPT. Deiodinase, Iodothyronine, Type II (DIO2, Accession NM\_013989) is another VGAM804 host target gene. DIO2 BINDING SITE1 and DIO2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DIO2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-



cleotide sequences of DIO2 BINDING SITE1 and DIO2 BINDING SITE2, designated SEQ ID:15176 and SEQ ID:6464 respectively, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31200] Another function of VGAM804 is therefore inhibition of Deiodinase, Iodothyronine, Type II (DIO2, Accession NM\_013989). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIO2. DKFZP434D193 (Accession XM\_114297) is another VGAM804 host target gene. DKFZP434D193 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434D193, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434D193 BINDING SITE, designated SEQ ID:42854, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31201] Another function of VGAM804 is therefore inhibition of DKFZP434D193 (Accession XM\_114297). Accordingly, utilities of VGAM804 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with DKFZP434D193. ESDN (Accession NM\_080927) is another VGAM804 host target gene. ESDN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESDN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESDN BINDING SITE, designated SEQ ID:28153, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31202] Another function of VGAM804 is therefore inhibition of ESDN (Accession NM\_080927). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESDN. FLJ10415 (Accession NM\_018089) is another VGAM804 host target gene. FLJ10415 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10415, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10415 BINDING SITE, designated SEQ ID:19853, to the nucleotide sequence of

VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31203] Another function of VGAM804 is therefore inhibition of FLJ10415 (Accession NM\_018089). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10415. FLJ10743 (Accession NM\_018201) is another VGAM804 host target gene. FLJ10743 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10743, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10743 BINDING SITE, designated SEQ ID:20083, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31204] Another function of VGAM804 is therefore inhibition of FLJ10743 (Accession NM\_018201). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10743. Gamma-aminobutyric Acid (GABA) B Receptor, 1 (GABBR1, Accession NM\_021903) is another VGAM804 host target gene. GABBR1 BINDING SITE is HOST TARGET binding site

found in the 5' untranslated region of mRNA encoded by GABBR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GABBR1 BINDING SITE, designated SEQ ID:22421, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31205] Another function of VGAM804 is therefore inhibition of Gamma-aminobutyric Acid (GABA) B Receptor, 1 (GABBR1, Accession NM\_021903). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GABBR1. HRD1 (Accession XM\_045498) is another VGAM804 host target gene. HRD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HRD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HRD1 BINDING SITE, designated SEQ ID:34471, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31206] Another function of VGAM804 is therefore inhibition of

HRD1 (Accession XM\_045498). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HRD1. HSPC063 (Accession NM\_014155) is another VGAM804 host target gene. HSPC063 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by HSPC063, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC063 BINDING SITE, designated SEQ ID:15440, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31207] Another function of VGAM804 is therefore inhibition of HSPC063 (Accession NM\_014155). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC063. ICB-1 (Accession NM\_004848) is another VGAM804 host target gene. ICB-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ICB-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of ICB-1 BINDING SITE, designated SEQ ID:11260, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31208] Another function of VGAM804 is therefore inhibition of ICB-1 (Accession NM\_004848). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ICB-1. KIAA0258 (Accession NM\_014785) is another VGAM804 host target gene. KIAA0258 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0258, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0258 BINDING SITE, designated SEQ ID:16653, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31209] Another function of VGAM804 is therefore inhibition of KIAA0258 (Accession NM\_014785). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0258. KIAA0326 (Accession XM\_034819) is another

VGAM804 host target gene. KIAA0326 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0326, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0326 BINDING SITE, designated SEQ ID:32162, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31210] Another function of VGAM804 is therefore inhibition of KIAA0326 (Accession XM\_034819). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0326. KIAA0495 (Accession XM\_031397) is another VGAM804 host target gene. KIAA0495 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0495, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0495 BINDING SITE, designated SEQ ID:31368, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31211] Another function of VGAM804 is therefore inhibition of KIAA0495 (Accession XM\_031397). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0495. KIAA1332 (Accession XM\_048774) is another VGAM804 host target gene. KIAA1332 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1332, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1332 BINDING SITE, designated SEQ ID:35263, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31212] Another function of VGAM804 is therefore inhibition of KIAA1332 (Accession XM\_048774). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1332. KIAA1962 (Accession XM\_088567) is another VGAM804 host target gene. KIAA1962 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1962, corresponding to a HOST TARGET binding site such as BINDING SITE I,



BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1962 BINDING SITE, designated SEQ ID:39835, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31213] Another function of VGAM804 is therefore inhibition of KIAA1962 (Accession XM\_088567). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1962. LAP1B (Accession XM\_035429) is another VGAM804 host target gene. LAP1B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LAP1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LAP1B BINDING SITE, designated SEQ ID:32265, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31214] Another function of VGAM804 is therefore inhibition of LAP1B (Accession XM\_035429). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LAP1B.

MGC15396 (Accession NM\_052855) is another VGAM804 host target gene. MGC15396 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC15396, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15396 BINDING SITE, designated SEQ ID:27437, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31215] Another function of VGAM804 is therefore inhibition of MGC15396 (Accession NM\_052855). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15396. MGC29891 (Accession NM\_144618) is another VGAM804 host target gene. MGC29891 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC29891, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC29891 BINDING SITE, designated SEQ ID:29440, to the nucleotide sequence of VGAM804 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3515.

[31216] Another function of VGAM804 is therefore inhibition of MGC29891 (Accession NM\_144618). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC29891. MGC4549 (Accession NM\_032377) is another VGAM804 host target gene. MGC4549 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4549, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4549 BINDING SITE, designated SEQ ID:26169, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31217] Another function of VGAM804 is therefore inhibition of MGC4549 (Accession NM\_032377). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4549. Neurogenic Differentiation 4 (NEUROD4, Accession NM\_021191) is another VGAM804 host target gene. NEUROD4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded

by NEUROD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEUROD4 BINDING SITE, designated SEQ ID:22169, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31218] Another function of VGAM804 is therefore inhibition of Neurogenic Differentiation 4 (NEUROD4, Accession NM\_021191). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEUROD4. PAS Domain Containing Serine/threonine Kinase (PASK, Accession NM\_015148) is another VGAM804 host target gene. PASK BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PASK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PASK BINDING SITE, designated SEQ ID:17504, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31219] Another function of VGAM804 is therefore inhibition of

PAS Domain Containing Serine/threonine Kinase (PASK, Accession NM\_015148). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PASK. Protein Phosphatase 4, Regulatory Subunit 1-like (PPP4R1L, Accession XM\_086650) is another VGAM804 host target gene. PPP4R1L BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PPP4R1L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP4R1L BINDING SITE, designated SEQ ID:38819, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31220] Another function of VGAM804 is therefore inhibition of Protein Phosphatase 4, Regulatory Subunit 1-like (PPP4R1L, Accession XM\_086650). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP4R1L. PRO2214 (Accession NM\_018517) is another VGAM804 host target gene. PRO2214 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA

encoded by PRO2214, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2214 BINDING SITE, designated SEQ ID:20590, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31221] Another function of VGAM804 is therefore inhibition of PRO2214 (Accession NM\_018517). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2214. SBB103 (Accession NM\_005785) is another VGAM804 host target gene. SBB103 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SBB103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SBB103 BINDING SITE, designated SEQ ID:12365, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31222] Another function of VGAM804 is therefore inhibition of SBB103 (Accession NM\_005785). Accordingly, utilities of

VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SBB103. Solute Carrier Family 25, (mitochondrial carrier), Member 18 (SLC25A18, Accession NM\_031481) is another VGAM804 host target gene. SLC25A18 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SLC25A18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC25A18 BINDING SITE, designated SEQ ID:25562, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31223] Another function of VGAM804 is therefore inhibition of Solute Carrier Family 25, (mitochondrial carrier), Member 18 (SLC25A18, Accession NM\_031481). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC25A18. SYNE-2 (Accession NM\_015180) is another VGAM804 host target gene. SYNE-2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SYNE-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYNE-2 BINDING SITE, designated SEQ ID:17533, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31224] Another function of VGAM804 is therefore inhibition of SYNE-2 (Accession NM\_015180). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYNE-2. Triple Homeobox 1 (TIX1, Accession XM\_029734) is another VGAM804 host target gene. TIX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIX1 BINDING SITE, designated SEQ ID:30932, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31225] Another function of VGAM804 is therefore inhibition of Triple Homeobox 1 (TIX1, Accession XM\_029734). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions as-



sociated with TIX1. LOC112868 (Accession XM\_053402) is another VGAM804 host target gene. LOC112868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC112868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC112868 BINDING SITE, designated SEQ ID:36085, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31226] Another function of VGAM804 is therefore inhibition of LOC112868 (Accession XM\_053402). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC112868. LOC130951 (Accession NM\_138804) is another VGAM804 host target gene. LOC130951 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130951, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130951 BINDING SITE, designated SEQ ID:29028, to the nucleotide sequence of VGAM804 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3515.

[31227] Another function of VGAM804 is therefore inhibition of LOC130951 (Accession NM\_138804). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130951. LOC144512 (Accession XM\_096623) is another VGAM804 host target gene. LOC144512 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC144512, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144512 BINDING SITE, designated SEQ ID:40429, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31228] Another function of VGAM804 is therefore inhibition of LOC144512 (Accession XM\_096623). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144512. LOC145773 (Accession XM\_085237) is another VGAM804 host target gene. LOC145773 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145773, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145773 BINDING SITE, designated SEQ ID:37982, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31229] Another function of VGAM804 is therefore inhibition of LOC145773 (Accession XM\_085237). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145773. LOC150848 (Accession XM\_097959) is another VGAM804 host target gene. LOC150848 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150848 BINDING SITE, designated SEQ ID:41261, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31230] Another function of VGAM804 is therefore inhibition of LOC150848 (Accession XM\_097959). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC150848. LOC157860 (Accession XM\_098832) is another VGAM804 host target gene. LOC157860 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC157860, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157860 BINDING SITE, designated SEQ ID:41863, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31231] Another function of VGAM804 is therefore inhibition of LOC157860 (Accession XM\_098832). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157860. LOC200609 (Accession XM\_117256) is another VGAM804 host target gene. LOC200609 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200609, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200609 BINDING SITE, designated SEQ ID:43337, to

the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31232] Another function of VGAM804 is therefore inhibition of LOC200609 (Accession XM\_117256). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200609. LOC219988 (Accession XM\_166223) is another VGAM804 host target gene. LOC219988 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219988, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219988 BINDING SITE, designated SEQ ID:44044, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31233] Another function of VGAM804 is therefore inhibition of LOC219988 (Accession XM\_166223). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219988. LOC221399 (Accession XM\_168134) is another VGAM804 host target gene. LOC221399 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC221399, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221399 BINDING SITE, designated SEQ ID:45050, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31234] Another function of VGAM804 is therefore inhibition of LOC221399 (Accession XM\_168134). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221399. LOC253675 (Accession XM\_172990) is another VGAM804 host target gene. LOC253675 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253675, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253675 BINDING SITE, designated SEQ ID:46267, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31235] Another function of VGAM804 is therefore inhibition of LOC253675 (Accession XM\_172990). Accordingly, utilities

of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253675. LOC253805 (Accession XM\_172854) is another VGAM804 host target gene. LOC253805 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253805, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253805 BINDING SITE, designated SEQ ID:46137, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31236] Another function of VGAM804 is therefore inhibition of LOC253805 (Accession XM\_172854). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253805. LOC254042 (Accession XM\_171022) is another VGAM804 host target gene. LOC254042 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254042, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC254042 BINDING SITE, designated SEQ ID:45793, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31237] Another function of VGAM804 is therefore inhibition of LOC254042 (Accession XM\_171022). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254042. LOC254143 (Accession XM\_172880) is another VGAM804 host target gene. LOC254143 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254143, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254143 BINDING SITE, designated SEQ ID:46158, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31238] Another function of VGAM804 is therefore inhibition of LOC254143 (Accession XM\_172880). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254143. LOC256942 (Accession XM\_170544) is another VGAM804 host target gene. LOC256942 BINDING



SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC256942, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256942 BINDING SITE, designated SEQ ID:45364, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31239] Another function of VGAM804 is therefore inhibition of LOC256942 (Accession XM\_170544). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256942. LOC57109 (Accession NM\_020385) is another VGAM804 host target gene. LOC57109 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC57109, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57109 BINDING SITE, designated SEQ ID:21657, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31240] Another function of VGAM804 is therefore inhibition of

LOC57109 (Accession NM\_020385). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57109. LOC91263 (Accession XM\_037264) is another VGAM804 host target gene. LOC91263 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91263, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91263 BINDING SITE, designated SEQ ID:32597, to the nucleotide sequence of VGAM804 RNA, herein designated VGAM RNA, also designated SEQ ID:3515.

[31241] Another function of VGAM804 is therefore inhibition of LOC91263 (Accession XM\_037264). Accordingly, utilities of VGAM804 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91263. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 805 (VGAM805) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[31242] VGAM805 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM805 was detected is described hereinabove with reference to Figs. 1–8.

[31243] VGAM805 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Feline Immunodeficiency Virus. VGAM805 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31244] VGAM805 gene encodes a VGAM805 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM805 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM805 precursor RNA is designated SEQ ID:791, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:791 is located at position 8793 relative to the genome of Feline Immunodeficiency Virus.

[31245] VGAM805 precursor RNA folds onto itself, forming VGAM805 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[31246] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM805 folded precursor RNA into VGAM805 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 48%) nucleotide se-  
quence of VGAM805 RNA is designated SEQ ID:3516, and  
is provided hereinbelow with reference to the sequence  
listing part.

[31247] VGAM805 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM805 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM805 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[31248] VGAM805 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM805 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM805 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM805 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM805 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[31249] The complementary binding of VGAM805 RNA, herein designated VGAM RNA, to host target binding sites on VGAM805 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM805 host target RNA into VGAM805 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31250] It is appreciated that VGAM805 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM805 host target genes. The mRNA of each one of this plurality of VGAM805 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM805 RNA, herein designated VGAM RNA, and which when bound by VGAM805 RNA causes inhibition of translation of respective one or more VGAM805 host target proteins.

[31251] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM805 gene, herein designated VGAM GENE, on one or

more VGAM805 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31252] It is yet further appreciated that a function of VGAM805 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of viral infection by Feline Immunodeficiency Virus. Specific functions, and accordingly utilities, of VGAM805 correlate with, and may be deduced from, the identity of the host target genes which VGAM805 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [31253] Nucleotide sequences of the VGAM805 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM805 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM805 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM805 are further described hereinbelow with reference to Table 1.
- [31254] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM805 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM805 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [31255] As mentioned hereinabove with reference to Fig. 1, a function of VGAM805 gene, herein designated VGAM is inhibition of expression of VGAM805 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM805 correlate with, and may be deduced from, the identity of the target genes which VGAM805 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [31256] BCL2-like 2 (BCL2L2, Accession NM\_004050) is a



VGAM805 host target gene. BCL2L2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL2L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2L2 BINDING SITE, designated SEQ ID:10265, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31257] A function of VGAM805 is therefore inhibition of BCL2-like 2 (BCL2L2, Accession NM\_004050), a gene which promotes cell survival. Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL2L2. The function of BCL2L2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM431. Integrin, Alpha 1 (ITGA1, Accession XM\_032902) is another VGAM805 host target gene. ITGA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of ITGA1 BINDING SITE, designated SEQ ID:31789, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31258] Another function of VGAM805 is therefore inhibition of Integrin, Alpha 1 (ITGA1, Accession XM\_032902). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGA1. Angiomotin Like 1 (AMOTL1, Accession XM\_057045) is another VGAM805 host target gene. AMOTL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AMOTL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AMOTL1 BINDING SITE, designated SEQ ID:36466, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31259] Another function of VGAM805 is therefore inhibition of Angiomotin Like 1 (AMOTL1, Accession XM\_057045). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with AMOTL1. Chromosome 20 Open Reading Frame 98 (C20orf98, Accession XM\_049398) is another VGAM805 host target gene. C20orf98 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C20orf98, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf98 BINDING SITE, designated SEQ ID:35418, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31260] Another function of VGAM805 is therefore inhibition of Chromosome 20 Open Reading Frame 98 (C20orf98, Accession XM\_049398). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf98. DKFZP762D096 (Accession XM\_037662) is another VGAM805 host target gene. DKFZP762D096 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP762D096, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DK-

FZP762D096 BINDING SITE, designated SEQ ID:32667, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31261] Another function of VGAM805 is therefore inhibition of DKFZP762D096 (Accession XM\_037662). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP762D096. Docking Protein 4 (DOK4, Accession NM\_018110) is another VGAM805 host target gene. DOK4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DOK4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DOK4 BINDING SITE, designated SEQ ID:19882, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31262] Another function of VGAM805 is therefore inhibition of Docking Protein 4 (DOK4, Accession NM\_018110). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DOK4. FLJ10043 (Accession NM\_017979) is another VGAM805 host target gene. FLJ10043 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ10043, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10043 BINDING SITE, designated SEQ ID:19707, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31263] Another function of VGAM805 is therefore inhibition of FLJ10043 (Accession NM\_017979). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10043. FLJ14743 (Accession XM\_042708) is another VGAM805 host target gene. FLJ14743 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14743, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14743 BINDING SITE, designated SEQ ID:33763, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31264] Another function of VGAM805 is therefore inhibition of

FLJ14743 (Accession XM\_042708). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14743. KIAA0889 (Accession NM\_015377) is another VGAM805 host target gene. KIAA0889 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0889, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0889 BINDING SITE, designated SEQ ID:17677, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31265] Another function of VGAM805 is therefore inhibition of KIAA0889 (Accession NM\_015377). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0889. MGC15476 (Accession NM\_145056) is another VGAM805 host target gene. MGC15476 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC15476, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of MGC15476 BINDING SITE, designated SEQ ID:29688, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31266] Another function of VGAM805 is therefore inhibition of MGC15476 (Accession NM\_145056). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15476. Phosphatidylinositol-4-phosphate 5-kinase, Type II, Beta (PIP5K2B, Accession NM\_003559) is another VGAM805 host target gene. PIP5K2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIP5K2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIP5K2B BINDING SITE, designated SEQ ID:9611, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31267] Another function of VGAM805 is therefore inhibition of Phosphatidylinositol-4-phosphate 5-kinase, Type II, Beta (PIP5K2B, Accession NM\_003559). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PIP5K2B. Retinoic Acid Induced 16 (RAI16, Accession NM\_022749) is another VGAM805 host target gene. RAI16 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RAI16, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAI16 BINDING SITE, designated SEQ ID:22970, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31268] Another function of VGAM805 is therefore inhibition of Retinoic Acid Induced 16 (RAI16, Accession NM\_022749). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAI16. LOC115297 (Accession XM\_053313) is another VGAM805 host target gene. LOC115297 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC115297, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115297 BINDING SITE, desig-



nated SEQ ID:36072, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31269] Another function of VGAM805 is therefore inhibition of LOC115297 (Accession XM\_053313). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115297. LOC146988 (Accession XM\_097150) is another VGAM805 host target gene. LOC146988 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146988, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146988 BINDING SITE, designated SEQ ID:40779, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31270] Another function of VGAM805 is therefore inhibition of LOC146988 (Accession XM\_097150). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146988. LOC254755 (Accession XM\_173224) is another VGAM805 host target gene. LOC254755 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254755, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254755 BINDING SITE, designated SEQ ID:46488, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31271] Another function of VGAM805 is therefore inhibition of LOC254755 (Accession XM\_173224). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254755. LOC51075 (Accession NM\_015959) is another VGAM805 host target gene. LOC51075 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51075, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51075 BINDING SITE, designated SEQ ID:18069, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31272] Another function of VGAM805 is therefore inhibition of

LOC51075 (Accession NM\_015959). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51075. LOC90072 (Accession XM\_028702) is another VGAM805 host target gene. LOC90072 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90072, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90072 BINDING SITE, designated SEQ ID:30728, to the nucleotide sequence of VGAM805 RNA, herein designated VGAM RNA, also designated SEQ ID:3516.

[31273] Another function of VGAM805 is therefore inhibition of LOC90072 (Accession XM\_028702). Accordingly, utilities of VGAM805 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90072. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 806 (VGAM806) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[31274] VGAM806 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM806 was detected is described hereinabove with reference to Figs. 1–8.

[31275] VGAM806 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus). VGAM806 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31276] VGAM806 gene encodes a VGAM806 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM806 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM806 precursor RNA is designated SEQ ID:792, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:792 is located at position 250093 relative to the genome of Shrimp White Spot Syndrome Virus (white spot bacilliform virus).

[31277] VGAM806 precursor RNA folds onto itself, forming VGAM806 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[31278] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM806 folded precursor RNA into VGAM806 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 80%) nucleotide se-  
quence of VGAM806 RNA is designated SEQ ID:3517, and  
is provided hereinbelow with reference to the sequence  
listing part.

[31279] VGAM806 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM806 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM806 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31280] VGAM806 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM806 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM806 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM806 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM806 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31281] The complementary binding of VGAM806 RNA, herein designated VGAM RNA, to host target binding sites on VGAM806 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM806 host target RNA into VGAM806 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31282] It is appreciated that VGAM806 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM806 host target genes. The mRNA of each one of this plurality of VGAM806 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM806 RNA, herein designated VGAM RNA, and which when bound by VGAM806 RNA causes inhibition of translation of respective one or more VGAM806 host target proteins.

[31283] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM806 gene, herein designated VGAM GENE, on one or more VGAM806 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31284] It is yet further appreciated that a function of VGAM806 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of viral infection by Shrimp White Spot Syndrome Virus (white spot bacilliform virus). Specific functions, and accordingly utilities, of VGAM806 correlate with, and may be deduced from, the identity of the host target genes which VGAM806 binds and inhibits, and the



function of these host target genes, as elaborated herein—below.

[31285] Nucleotide sequences of the VGAM806 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM806 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM806 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM806 are further described hereinbelow with reference to Table 1.

[31286] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM806 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM806 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31287] As mentioned hereinabove with reference to Fig. 1, a function of VGAM806 gene, herein designated VGAM is inhibition of expression of VGAM806 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM806 correlate with, and may be deduced from, the identity of the target genes which VGAM806 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[31288] Adrenergic, Beta, Receptor Kinase 2 (ADRBK2, Accession NM\_005160) is a VGAM806 host target gene. ADRBK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADRBK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADRBK2 BINDING SITE, designated SEQ ID:11643, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31289] A function of VGAM806 is therefore inhibition of Adrenergic, Beta, Receptor Kinase 2 (ADRBK2, Accession NM\_005160), a gene which regulates desensitization of G protein-coupled receptors. Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADRBK2. The function of ADRBK2 has been established by previous studies. In the rat and the mouse, Benovic et al. (1991) identified a second beta-adrenergic receptor kinase. See beta-adrenergic receptor kinase-1 (ADRBK1; 109635). They isolated the receptor by screening a bovine brain

cDNA library with a catalytic domain fragment of the beta-adrenergic receptor kinase. The enzyme, which they termed BARK2, showed overall amino acid identity of 85% with BARK1, with the protein kinase catalytic domain having 95% identity. In the rat, BARK2 mRNA was localized predominantly in neuronal tissues, although low levels were also observed in various tissues. The gene encoding BARK2 mapped to mouse chromosome 5, whereas that encoding BARK1 was localized to mouse chromosome 19. This may indicate that the ADRBK2 gene is located on human chromosome 4 or chromosome 7 since these show extensive homology of synteny with mouse chromosome 5. In fact, however, Calabrese et al. (1994) demonstrated by fluorescence in situ hybridization that the ADRBK2 gene is located on human 22q11.

[31290] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31291] Benovic, J. L.; Onorato, J. J.; Arriza, J. L.; Stone, W. C.; Lohse, M.; Jenkins, N. A.; Gilbert, D. J.; Copeland, N. G.; Caron, M. G.; Lefkowitz, R. J. : Cloning, expression, and chromosomal localization of beta-adrenergic receptor kinase 2: a new member of the receptor kinase family. J.

Biol. Chem. 266: 14939–14946, 1991. ; and

[31292] Calabrese, G.; Sallese, M.; Stornaiuolo, A.; Stuppia, L.; Palka, G.; De Blasi, A. : Chromosome mapping of the human arrestin (SAG), beta-arrestin 2 (ARRB2), and beta-adrenergic receptor.

[31293] Further studies establishing the function and utilities of ADRBK2 are found in John Hopkins OMIM database record ID 109636, and in cited publications numbered 145 and 5931 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Exostoses (multiple)-like 1 (EXTL1, Accession NM\_004455) is another VGAM806 host target gene. EXTL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EXTL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EXTL1 BINDING SITE, designated SEQ ID:10754, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31294] Another function of VGAM806 is therefore inhibition of Exostoses (multiple)-like 1 (EXTL1, Accession NM\_004455), a gene which probably contribute to the

synthesis of heparan sulfate and heparin. Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EXTL1. The function of EXTL1 has been established by previous studies. The tumor suppressors EXT1 (OMIM Ref. No. 133700) and EXT2 (OMIM Ref. No. 133701) are associated with hereditary multiple exostoses and encode bifunctional glycosyltransferases essential for chain polymerization of heparan sulfate and its analog, heparin. Wise et al. (1997) identified another gene, termed EXTL by them, that showed striking sequence similarity to both EXT1 and EXT2 at the nucleotide and amino acid sequence levels. Although the mRNA transcribed from this gene is similar in size to that of EXT1 and EXT2, its pattern of expression was quite different. Of the 3 highly homologous EXT-like genes, EXTL1, EXTL2 (OMIM Ref. No. 602411), and EXTL3 (OMIM Ref. No. 605744), EXTL2 is an alpha-1,4-GlcNAc transferase I, the key enzyme that initiates the heparan sulfate/heparin synthesis. Kim et al. (2001) transiently expressed truncated forms of EXTL1 and EXTL3, lacking the putative NH<sub>2</sub>-terminal transmembrane and cytoplasmic domains, in COS-1 cells and found that the cells harbored alpha-GlcNAc transferase activity. Various

results suggested that EXTL3 is most likely involved in both chain initiation and elongation, whereas EXTL1 is possibly involved only in the chain elongation of heparan sulfate, and perhaps of heparin as well. Thus, the acceptor specificities of the 5 family members are overlapping but distinct, except for EXT1 and EXT2, which have the same specificity. Thus, all of the 5 cloned human EXT gene family proteins harbor glycosyltransferase activities, which probably contribute to the synthesis of heparan sulfate and heparin. Xu et al. (1999) examined the EXTL1 and EXTL2 genes for the presence of germline mutations in hereditary multiple exostosis patients and found none. Hall et al. (2002) proposed the EXTL genes as candidates for second mutations leading to the development of exostoses. By radiation hybrid analysis and by fluorescence in situ hybridization, Wise et al. (1997) mapped EXTL to 1p36.1 between D1S458 and D1S511, a region that frequently shows loss of heterozygosity in a variety of tumor types.

[31295] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31296] Wise, C. A.; Clines, G. A.; Massa, H.; Trask, B. J.; Lovett, M.

: Identification and localization of the gene for EXTL, a third member of the multiple exostoses gene family.

Genome Res. 7: 10–16, 1997. ; and

[31297] Kim, B.-T.; Kitagawa, H.; Tamura, J.; Saito, T.; Kusche-Gullberg, M.; Lindahl, U.; Sugahara, K. : Human tumor suppressor EXT gene family members EXTL1 and EXTL3 encode alpha-1,4-N-acetyl.

[31298] Further studies establishing the function and utilities of EXTL1 are found in John Hopkins OMIM database record ID 601738, and in cited publications numbered 3588, 9324–932 and 11784 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. G Protein-coupled Receptor 65 (GPR65, Accession XM\_007392) is another VGAM806 host target gene. GPR65 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GPR65, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR65 BINDING SITE, designated SEQ ID:30052, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31299] Another function of VGAM806 is therefore inhibition of G Protein-coupled Receptor 65 (GPR65, Accession XM\_007392). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR65. Podocalyxin-like (PODXL, Accession NM\_005397) is another VGAM806 host target gene. PODXL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PODXL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PODXL BINDING SITE, designated SEQ ID:11869, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31300] Another function of VGAM806 is therefore inhibition of Podocalyxin-like (PODXL, Accession NM\_005397), a gene which is an antiadhesin. Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PODXL. The function of PODXL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to



VGAM247.TSLP (Accession NM\_033035) is another VGAM806 host target gene. TSLP BINDING SITE1 and TSLP BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TSLP, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSLP BINDING SITE1 and TSLP BINDING SITE2, designated SEQ ID:26928 and SEQ ID:28848 respectively, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31301] Another function of VGAM806 is therefore inhibition of TSLP (Accession NM\_033035), a gene which may contribute directly to the activation of Langerhans cells and inhibit apoptosis. Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSLP. The function of TSLP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM558.Chromosome 20 Open Reading Frame 121 (C20orf121, Accession NM\_024331) is another VGAM806 host target gene. C20orf121 BINDING SITE is HOST TAR-

GET binding site found in the 3' untranslated region of mRNA encoded by C20orf121, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf121 BINDING SITE, designated SEQ ID:23628, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31302] Another function of VGAM806 is therefore inhibition of Chromosome 20 Open Reading Frame 121 (C20orf121, Accession NM\_024331). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf121. Chromosome 8 Open Reading Frame 14 (C8orf14, Accession NM\_054029) is another VGAM806 host target gene. C8orf14 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C8orf14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C8orf14 BINDING SITE, designated SEQ ID:27639, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ

ID:3517.

[31303] Another function of VGAM806 is therefore inhibition of Chromosome 8 Open Reading Frame 14 (C8orf14, Accession NM\_054029). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C8orf14. FLJ11274 (Accession NM\_018375) is another VGAM806 host target gene. FLJ11274 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ11274, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11274 BINDING SITE, designated SEQ ID:20399, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31304] Another function of VGAM806 is therefore inhibition of FLJ11274 (Accession NM\_018375). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11274. FLJ21657 (Accession NM\_022483) is another VGAM806 host target gene. FLJ21657 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ21657, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21657 BINDING SITE, designated SEQ ID:22857, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31305] Another function of VGAM806 is therefore inhibition of FLJ21657 (Accession NM\_022483). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21657. FLJ32334 (Accession NM\_144565) is another VGAM806 host target gene. FLJ32334 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ32334, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32334 BINDING SITE, designated SEQ ID:29368, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31306] Another function of VGAM806 is therefore inhibition of FLJ32334 (Accession NM\_144565). Accordingly, utilities of

VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32334. Protein-kinase, Interferon-inducible Double Stranded RNA Dependent Inhibitor, Repressor of (P58 repressor) (PRKRIR, Accession NM\_004705) is another VGAM806 host target gene. PRKRIR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRKRIR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKRIR BINDING SITE, designated SEQ ID:11051, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31307] Another function of VGAM806 is therefore inhibition of Protein-kinase, Interferon-inducible Double Stranded RNA Dependent Inhibitor, Repressor of (P58 repressor) (PRKRIR, Accession NM\_004705). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKRIR. Solute Carrier Family 26, Member 7 (SLC26A7, Accession NM\_052832) is another VGAM806 host target gene. SLC26A7 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by SLC26A7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC26A7 BINDING SITE, designated SEQ ID:27414, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31308] Another function of VGAM806 is therefore inhibition of Solute Carrier Family 26, Member 7 (SLC26A7, Accession NM\_052832). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC26A7. UBX Domain Containing 2 (UBXD2, Accession XM\_043196) is another VGAM806 host target gene. UBXD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBXD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBXD2 BINDING SITE, designated SEQ ID:33911, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31309] Another function of VGAM806 is therefore inhibition of UBX Domain Containing 2 (UBXD2, Accession XM\_043196). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBXD2. LOC144473 (Accession XM\_096606) is another VGAM806 host target gene. LOC144473 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144473, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144473 BINDING SITE, designated SEQ ID:40413, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31310] Another function of VGAM806 is therefore inhibition of LOC144473 (Accession XM\_096606). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144473. LOC152345 (Accession XM\_087442) is another VGAM806 host target gene. LOC152345 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152345, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152345 BINDING SITE, designated SEQ ID:39265, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31311] Another function of VGAM806 is therefore inhibition of LOC152345 (Accession XM\_087442). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152345. LOC222678 (Accession XM\_167111) is another VGAM806 host target gene. LOC222678 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC222678, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222678 BINDING SITE, designated SEQ ID:44605, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31312] Another function of VGAM806 is therefore inhibition of LOC222678 (Accession XM\_167111). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with LOC222678. LOC91796 (Accession XM\_040743) is another VGAM806 host target gene. LOC91796 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91796, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91796 BINDING SITE, designated SEQ ID:33372, to the nucleotide sequence of VGAM806 RNA, herein designated VGAM RNA, also designated SEQ ID:3517.

[31313] Another function of VGAM806 is therefore inhibition of LOC91796 (Accession XM\_040743). Accordingly, utilities of VGAM806 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91796. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 807 (VGAM807) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31314] VGAM807 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM807 was detected is described hereinabove with reference to Figs. 1–8.

[31315] VGAM807 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 2. VGAM807 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31316] VGAM807 gene encodes a VGAM807 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM807 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM807 precursor RNA is designated SEQ ID:793, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:793 is located at position 61419 relative to the genome of Equine Herpesvirus 2.

[31317] VGAM807 precursor RNA folds onto itself, forming VGAM807 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31318] An enzyme complex designated DICER COMPLEX, `dices` the VGAM807 folded precursor RNA into VGAM807 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM807 RNA is designated SEQ ID:3518, and is provided hereinbelow with reference to the sequence listing part.

[31319] VGAM807 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM807 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM807 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31320] VGAM807 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM807 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM807 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM807 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM807 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31321] The complementary binding of VGAM807 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM807 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM807 host target RNA into VGAM807 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31322] It is appreciated that VGAM807 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM807 host target genes. The mRNA of each one of this plurality of VGAM807 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM807 RNA, herein designated VGAM RNA, and which when bound by VGAM807 RNA causes inhibition of translation of respective one or more VGAM807 host target proteins.

[31323] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM807 gene, herein designated VGAM GENE, on one or more VGAM807 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31324] It is yet further appreciated that a function of VGAM807 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM807 correlate with, and may be deduced from, the identity of the host target genes which VGAM807 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31325] Nucleotide sequences of the VGAM807 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

5' duced 5' VGAM807 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM807 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM807 are further described hereinbelow with reference to Table 1.

[31326] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM807 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM807 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31327] As mentioned hereinabove with reference to Fig. 1, a function of VGAM807 gene, herein designated VGAM is inhibition of expression of VGAM807 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM807 correlate with, and may be deduced from, the identity of the target genes which VGAM807 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31328] Adenylate Cyclase 7 (ADCY7, Accession NM\_001114) is a VGAM807 host target gene. ADCY7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by ADCY7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADCY7 BINDING SITE, designated SEQ ID:6781, to the nucleotide sequence of VGAM807 RNA, herein designated VGAM RNA, also designated SEQ ID:3518.

[31329] A function of VGAM807 is therefore inhibition of Adenylate Cyclase 7 (ADCY7, Accession NM\_001114), a gene which is a membrane-bound,  $Ca^{2+}$ -inhibitable adenylyl cyclase. Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADCY7. The function of ADCY7 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM108. Calmodulin 3 (phosphorylase kinase, delta) (CALM3, Accession NM\_005184) is another VGAM807 host target gene. CALM3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CALM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the



nucleotide sequences of CALM3 BINDING SITE, designated SEQ ID:11685, to the nucleotide sequence of VGAM807 RNA, herein designated VGAM RNA, also designated SEQ ID:3518.

[31330] Another function of VGAM807 is therefore inhibition of Calmodulin 3 (phosphorylase kinase, delta) (CALM3, Accession NM\_005184), a gene which mediates the control of a large number of enzymes by  $Ca^{++}$ . Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CALM3. The function of CALM3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM785. Cyclin-dependent Kinase 5, Regulatory Subunit 2 (p39) (CDK5R2, Accession NM\_003936) is another VGAM807 host target gene. CDK5R2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDK5R2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDK5R2 BINDING SITE, designated SEQ ID:10041, to the nucleotide sequence of VGAM807 RNA,

herein designated VGAM RNA, also designated SEQ ID:3518.

[31331] Another function of VGAM807 is therefore inhibition of Cyclin-dependent Kinase 5, Regulatory Subunit 2 (p39) (CDK5R2, Accession NM\_003936), a gene which acts as a regulatory subunit for the cyclin-dependent CDK5. Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDK5R2. The function of CDK5R2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM403. Microtubule-associated Protein 1A (MAP1A, Accession NM\_002373) is another VGAM807 host target gene. MAP1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAP1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP1A BINDING SITE, designated SEQ ID:8182, to the nucleotide sequence of VGAM807 RNA, herein designated VGAM RNA, also designated SEQ ID:3518.

[31332] Another function of VGAM807 is therefore inhibition of Microtubule-associated Protein 1A (MAP1A, Accession NM\_002373), a gene which is a structural protein involved in the filamentous cross-bridging between microtubules and other skeletal elements. Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP1A. The function of MAP1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM315. Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3, Accession NM\_004273) is another VGAM807 host target gene. CHST3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CHST3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHST3 BINDING SITE, designated SEQ ID:10476, to the nucleotide sequence of VGAM807 RNA, herein designated VGAM RNA, also designated SEQ ID:3518.

[31333] Another function of VGAM807 is therefore inhibition of Carbohydrate (chondroitin 6) Sulfotransferase 3 (CHST3,

Accession NM\_004273). Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHST3. FLJ10350 (Accession XM\_170946) is another VGAM807 host target gene. FLJ10350 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10350 BINDING SITE, designated SEQ ID:45729, to the nucleotide sequence of VGAM807 RNA, herein designated VGAM RNA, also designated SEQ ID:3518.

[31334] Another function of VGAM807 is therefore inhibition of FLJ10350 (Accession XM\_170946). Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10350. Transducin (beta)-like 1Y-linked (TBL1Y, Accession NM\_033284) is another VGAM807 host target gene. TBL1Y BINDING SITE1 through TBL1Y BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TBL1Y, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBL1Y BINDING SITE1 through TBL1Y BINDING SITE3, designated SEQ ID:27099, SEQ ID:28609 and SEQ ID:28610 respectively, to the nucleotide sequence of VGAM807 RNA, herein designated VGAM RNA, also designated SEQ ID:3518.

[31335] Another function of VGAM807 is therefore inhibition of Transducin (beta)-like 1Y-linked (TBL1Y, Accession NM\_033284). Accordingly, utilities of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TBL1Y. LOC125268 (Accession XM\_071960) is another VGAM807 host target gene. LOC125268 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC125268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC125268 BINDING SITE, designated SEQ ID:37449, to the nucleotide sequence of VGAM807 RNA, herein designated VGAM RNA, also designated SEQ ID:3518.

[31336] Another function of VGAM807 is therefore inhibition of LOC125268 (Accession XM\_071960). Accordingly, utilities

of VGAM807 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125268. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 808 (VGAM808) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31337] VGAM808 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM808 was detected is described hereinabove with reference to Figs. 1–8.

[31338] VGAM808 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 2. VGAM808 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31339] VGAM808 gene encodes a VGAM808 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM808 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM808 precursor RNA is designated SEQ ID:794, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:794 is located at position 60546 relative to the genome of Equine Herpesvirus 2.

[31340] VGAM808 precursor RNA folds onto itself, forming VGAM808 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31341] An enzyme complex designated DICER COMPLEX, `dices` the VGAM808 folded precursor RNA into VGAM808 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM808 RNA is designated SEQ ID:3519, and

is provided hereinbelow with reference to the sequence listing part.

[31342] VGAM808 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM808 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM808 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31343] VGAM808 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM808 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM808 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-



ing – VGAM808 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM808 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31344] The complementary binding of VGAM808 RNA, herein designated VGAM RNA, to host target binding sites on VGAM808 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM808 host target RNA into VGAM808 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31345] It is appreciated that VGAM808 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM808 host target genes. The mRNA of each one of this plurality of VGAM808 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM808 RNA, herein designated VGAM RNA, and which when bound by VGAM808 RNA causes inhibition of translation of respective one or more VGAM808 host target proteins.

[31346] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM808 gene, herein designated VGAM GENE, on one or more VGAM808 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31347] It is yet further appreciated that a function of VGAM808 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM808 correlate with, and may be deduced from, the identity of the host target genes which VGAM808 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31348] Nucleotide sequences of the VGAM808 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM808 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM808 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM808 are further described hereinbelow with reference to Table 1.

[31349] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM808 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM808 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31350] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM808 gene, herein designated VGAM is inhibition of expression of VGAM808 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM808 correlate with, and may be deduced from, the identity of the target genes which VGAM808 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31351] Absent In Melanoma 1 (AIM1, Accession XM\_166300) is a VGAM808 host target gene. AIM1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by AIM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AIM1 BINDING SITE, designated SEQ ID:44114, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31352] A function of VGAM808 is therefore inhibition of Absent In Melanoma 1 (AIM1, Accession XM\_166300), a gene which interactions with the cytoskeleton. Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AIM1. The function of AIM1 has been established by previous stud-

ies. The AIM1 gene encodes a melanocyte differentiation antigen that is expressed in a high percentage of melanoma cell lines. Its homolog in medaka, 'B,' encodes a transporter that mediates melanin synthesis. Harada et al. (2001) identified an antigen in human melanoma that they called AIM1 protein. The AIM1 gene was expressed in 3 melanoma cell lines, but not in a fibroblast cell line, and not at significant levels in any of 15 normal tissues. The human AIM1 gene encodes a protein of 530 amino acids. Northern blot analysis detected 2 transcripts, one of 1.7 kb and the other of 2.8 kb. Harada et al. (2001) concluded that the AIM1 gene encodes a melanocyte differentiation antigen that is expressed in a high percentage of melanoma cell lines. By sequence analysis, Newton et al. (2001) mapped the MATP gene to chromosome 5p.

[31353] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31354] Harada, M.; Li, Y. F.; El-Gamil, M.; Rosenberg, S. A.; Robbins, P. F. : Use of an in vitro immunoselected tumor line to identify shared melanoma antigens recognized by HLA-A\*0201-restricted T cells. Cancer Res. 61: 1089-1094, 2001. ; and

[31355] Newton, J. M.; Cohen-Barak, O.; Hagiwara, N.; Gardner, J. M.; Davisson, M. T.; King, R. A.; Brilliant, M. H. : Mutations in the human orthologue of the mouse underwhite gene (uw) underl.

[31356] Further studies establishing the function and utilities of AIM1 are found in John Hopkins OMIM database record ID 606202, and in cited publications numbered 904–906 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. EphB4 (EPHB4, Accession NM\_004444) is another VGAM808 host target gene. EPHB4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPHB4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPHB4 BINDING SITE, designated SEQ ID:10738, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31357] Another function of VGAM808 is therefore inhibition of EphB4 (EPHB4, Accession NM\_004444), a gene which receptor for members of the ephrin-b family. binds to ephrin-b2. Accordingly, utilities of VGAM808 include di-

agnosis, prevention and treatment of diseases and clinical conditions associated with EPHB4. The function of EPHB4 has been established by previous studies. See 179610 for background on Eph receptors and their ligands, the ephrins. In CD34+ human bone marrow cells and a human hepatocellular carcinoma cell line, Bennett et al. (1994) identified a novel transmembrane tyrosine kinase, which they called hepatoma transmembrane kinase, or HTK. They reported that the predicted 987-amino acid sequence of HTK includes a transmembrane region and signal sequence. The predicted extracellular domain contains a cysteine-rich region and tandem fibronectin type III repeats, while the intracellular domain contains the catalytic domain. Northern blot analysis demonstrated a single HTK transcript abundantly expressed in placenta and in a range of primary tissues and malignant cell lines. It is expressed in fetal, but not adult, brain, and in primitive and myeloid, but not lymphoid, hematopoietic cells. The protein shared amino acid similarity with the Eph subfamily of tyrosine kinases. Using 2 independent sets of primers specific for human HTK to amplify DNA from a panel of human-hamster hybrid cell lines, they demonstrated that the human gene is located on chromosome 7. Berclaz et

al. (1996) examined the expression of HTK in normal and malignant breast tissue. They found that in normal breast, expression is confined to secretory luminal epithelial cells. They found elevated expression of HTK in several human breast carcinoma cell lines as well as in primary ductal carcinomas of the breast. The authors suggested that HTK may have a role in the differentiation or maintenance of secretory epithelia. Gerety et al. (1999) generated mice with a targeted disruption of EphB4 by introducing a tau-lacZ marker into the gene. Unlike the broadly expressed ephrin B2 gene (EFNB2; 600527), EphB4 is uniquely expressed in vascular endothelial and endocardial cells. The authors' analysis also confirmed that EphB4 is preferentially expressed on veins. Remarkably, the phenotype of homozygous EphB4 mutants was virtually symmetric to that of EfnB2 mutants. These data identified EphB4 as the major essential interaction partner of EFNB2 in angiogenesis and further indicated that the requisite function of this receptor is intrinsic to the circulatory system. In addition, these data indicated that EFNB2 and EphB4 mediate reciprocal interactions between arteries and veins that are essential for proper angiogenic remodeling of the capillary beds.



[31358] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31359] Bennett, B. D.; Wang, Z.; Kuang, W.-J.; Wang, A.; Groopman, J. E.; Goeddel, D. V.; Scadden, D. T. : Cloning and characterization of HTK, a novel transmembrane tyrosine kinase of the EPH subfamily. J. Biol. Chem. 269: 14211–14218, 1994. ; and

[31360] Gerety, S. S.; Wang, H. U.; Chen, Z.-F.; Anderson, D. J. : Symmetrical mutant phenotypes of the receptor EphB4 and its specific transmembrane ligand ephrin-B2 in cardiovascular developme.

[31361] Further studies establishing the function and utilities of EPHB4 are found in John Hopkins OMIM database record ID 600011, and in cited publications numbered 8346–8348 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Homeo Box A3 (HOXA3, Accession NM\_030661) is another VGAM808 host target gene. HOXA3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HOXA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of HOXA3 BINDING SITE, designated SEQ ID:24993, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31362] Another function of VGAM808 is therefore inhibition of Homeo Box A3 (HOXA3, Accession NM\_030661). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HOXA3. Tenascin C (hexabrachion) (TNC, Accession NM\_002160) is another VGAM808 host target gene. TNC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNC BINDING SITE, designated SEQ ID:7935, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31363] Another function of VGAM808 is therefore inhibition of Tenascin C (hexabrachion) (TNC, Accession NM\_002160), a gene which has epidermal growth factor-like repeats. Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with TNC. The function of TNC has been established by previous studies. Tenascin, also known as hexabrachion and cytotactin, is an extracellular matrix protein with a spatially and temporally restricted tissue distribution. It is a hexomeric, multidomain protein with disulfide-linked subunits of 190 to 240 kD, originally characterized as 'myotendinous antigen.' In the embryo it is present in dense mesenchyme surrounding developing epithelia, in tendon anlagen, and in developing cartilage and bone. In the adult tenascin remains present in tendons and myotendinous junctions in the perichondrium and periosteum, as well as in smooth muscle. Pearson et al. (1988) isolated cDNA clones coding for tenascin from a chicken fibroblast cDNA expression library using a specific tenascin antiserum. They showed induction of tenascin in vitro by fetal calf serum as well as by transforming growth factor-beta (OMIM Ref. No. 190180). The gene is also called hexabrachion (HXB). Olson and Srivastava (1996) reviewed processes involved in separation of the cardiac tube into the atria, ventricles, and outflow tract. They noted that tenascin is upregulated and NCAM (OMIM Ref. No. 116930) is downregulated in the embryonic endocardial cushions. This upregulation of tenascin

is thought to disrupt cell substrate adhesion and to allow cells to migrate through the extracellular component of the cardiac cushion. Olson and Srivastava (1996) suggested that abnormalities or arrests in these processes may be responsible for some of the AV canal and conotruncal defects in infants. Animal model experiments lend further support to the function of TNC. In the central nervous system, tenascin C is expressed primarily by astrocytes. Tenascin is precisely localized in the vibrissae-related barrel fields of the developing somatosensory cortex, suggesting that it may be important in the formation of barrel boundaries. Steindler et al. (1995) demonstrated normal barrels in homozygous knockout mice for tenascin C, finding no abnormalities of the barrel boundaries despite the absence of this molecule. However, Mitrovic and Schachner (1995) were able to detect tenascin C immunoreactivity, albeit in an abnormal pattern, in the knockout mice designed to be null mutants for tenascin C expression.

[31364] It is appreciated that the abovementioned animal model for TNC is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[31365] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31366] Olson, E.; Srivastava, D. : Molecular pathways controlling heart development. Science 272: 671–676, 1996. ; and

[31367] Steindler, D. A.; Settles, D.; Erickson, H. P.; Laywell, E. D.; Yoshiki, A.; Faissner, A.; Kusakabe, M. : Tenascin knock-out mice: barrels, boundary molecules, and glial scars. J. Neurosc.

[31368] Further studies establishing the function and utilities of TNC are found in John Hopkins OMIM database record ID 187380, and in cited publications numbered 12678–12682, 12341–59 and 10840 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DKFZP434G1415 (Accession NM\_031292) is another VGAM808 host target gene. DKFZP434G1415 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434G1415, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434G1415 BINDING SITE, designated SEQ ID:25315, to the nucleotide sequence of

VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31369] Another function of VGAM808 is therefore inhibition of DKFZP434G1415 (Accession NM\_031292). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434G1415. FLJ10508 (Accession NM\_018118) is another VGAM808 host target gene. FLJ10508 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10508, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10508 BINDING SITE, designated SEQ ID:19894, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31370] Another function of VGAM808 is therefore inhibition of FLJ10508 (Accession NM\_018118). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10508. FLJ14708 (Accession NM\_032827) is another VGAM808 host target gene. FLJ14708 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ14708, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14708 BINDING SITE, designated SEQ ID:26600, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31371] Another function of VGAM808 is therefore inhibition of FLJ14708 (Accession NM\_032827). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14708. KIAA0930 (Accession XM\_047214) is another VGAM808 host target gene. KIAA0930 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0930, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0930 BINDING SITE, designated SEQ ID:34917, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31372] Another function of VGAM808 is therefore inhibition of KIAA0930 (Accession XM\_047214). Accordingly, utilities

of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0930. KIAA1655 (Accession XM\_039442) is another VGAM808 host target gene. KIAA1655 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1655, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1655 BINDING SITE, designated SEQ ID:33085, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31373] Another function of VGAM808 is therefore inhibition of KIAA1655 (Accession XM\_039442). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1655. KIAA1924 (Accession XM\_057091) is another VGAM808 host target gene. KIAA1924 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1924, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of



KIAA1924 BINDING SITE, designated SEQ ID:36478, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31374] Another function of VGAM808 is therefore inhibition of KIAA1924 (Accession XM\_057091). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1924. LPS-responsive Vesicle Trafficking, Beach and Anchor Containing (LRBA, Accession NM\_006726) is another VGAM808 host target gene. LRBA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LRBA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRBA BINDING SITE, designated SEQ ID:13556, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31375] Another function of VGAM808 is therefore inhibition of LPS-responsive Vesicle Trafficking, Beach and Anchor Containing (LRBA, Accession NM\_006726). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with LRBA. MGC9753 (Accession NM\_033419) is another VGAM808 host target gene. MGC9753 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGC9753, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC9753 BINDING SITE, designated SEQ ID:27240, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31376] Another function of VGAM808 is therefore inhibition of MGC9753 (Accession NM\_033419). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC9753. Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4C (SEMA4C, Accession NM\_017789) is another VGAM808 host target gene. SEMA4C BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SEMA4C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

SEMA4C BINDING SITE, designated SEQ ID:19421, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31377] Another function of VGAM808 is therefore inhibition of Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4C (SEMA4C, Accession NM\_017789). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA4C. LOC255631 (Accession XM\_171267) is another VGAM808 host target gene.

LOC255631 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255631, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255631 BINDING SITE, designated SEQ ID:46038, to the nucleotide sequence of VGAM808 RNA, herein designated VGAM RNA, also designated SEQ ID:3519.

[31378] Another function of VGAM808 is therefore inhibition of LOC255631 (Accession XM\_171267). Accordingly, utilities of VGAM808 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC255631. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 809 (VGAM809) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31379] VGAM809 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM809 was detected is described hereinabove with reference to Figs. 1–8.

[31380] VGAM809 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 2. VGAM809 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31381] VGAM809 gene encodes a VGAM809 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM809 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM809 precursor RNA is designated SEQ

ID:795, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:795 is located at position 60052 relative to the genome of Equine Herpesvirus 2.

[31382] VGAM809 precursor RNA folds onto itself, forming VGAM809 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31383] An enzyme complex designated DICER COMPLEX, `dices` the VGAM809 folded precursor RNA into VGAM809 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM809 RNA is designated SEQ ID:3520, and is provided hereinbelow with reference to the sequence

listing part.

[31384] VGAM809 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM809 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM809 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31385] VGAM809 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM809 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM809 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM809 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM809 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31386] The complementary binding of VGAM809 RNA, herein designated VGAM RNA, to host target binding sites on VGAM809 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM809 host target RNA into VGAM809 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31387] It is appreciated that VGAM809 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM809 host target genes. The mRNA of each one of this plurality of VGAM809 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM809 RNA, herein designated VGAM

RNA, and which when bound by VGAM809 RNA causes inhibition of translation of respective one or more VGAM809 host target proteins.

[31388] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM809 gene, herein designated VGAM GENE, on one or more VGAM809 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31389] It is yet further appreciated that a function of VGAM809 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,



utilities of VGAM809 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM809 correlate with, and may be deduced from, the identity of the host target genes which VGAM809 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31390] Nucleotide sequences of the VGAM809 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM809 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM809 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM809 are further described hereinbelow with reference to Table 1.

[31391] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM809 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM809 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31392] As mentioned hereinabove with reference to Fig. 1, a function of VGAM809 gene, herein designated VGAM is

inhibition of expression of VGAM809 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM809 correlate with, and may be deduced from, the identity of the target genes which VGAM809 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31393] A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 4 (ADAMTS4, Accession NM\_005099) is a VGAM809 host target gene. ADAMTS4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ADAMTS4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAMTS4 BINDING SITE, designated SEQ ID:11566, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31394] A function of VGAM809 is therefore inhibition of A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 4 (ADAMTS4, Accession NM\_005099), a gene which cleaves aggrecan, a cartilage proteoglycan, and may be involved in its turnover. Ac-

cordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAMTS4. The function of ADAMTS4 has been established by previous studies. Aggrecan degradation is an important factor in the erosion of articular cartilage in arthritic diseases. This degradation involves proteolysis of the aggrecan core protein near the N terminus, where 2 major cleavage sites have been identified. Matrix metalloproteinases (MMPs) cleave aggrecan between asn341 and phe342. Aggrecanase cleaves aggrecan between glu373 and ala374. Tortorella et al. (1999) purified and partially sequenced bovine aggrecanase-1. By PCR with primers designed from a highly homologous murine EST, they cloned sequences from the homologous human cDNA. They assembled a full-length open reading frame from this initial human PCR product and from another human EST. The human aggrecanase-1 (ADAMTS4) open reading frame encodes an 837-amino acid protein with a signal sequence, a propeptide domain, a catalytic domain, a disintegrin-like domain, and a C-terminal domain with a thrombospondin (TSP) type 1 motif. There is a conserved zinc-binding domain and a furin-sensitive sequence. The presence of a probable cysteine switch sequence in ag-

aggrecanase-1 suggested that, like the MMPs, it is synthesized as a zymogen and is cleaved to remove the propeptide domain and generate the mature active enzyme. A cloned portion of the bovine aggrecanase-1 cDNA was 94% homologous to the human cDNA. Human aggre-canase-1 cleaved bovine aggrecan between the glu373-ala374, but not the asn341-phe342, bond. Tortorella et al. (1999) stated that ADAMTS4 mRNA is present in brain, lung, and heart, and at very low levels in placenta and muscle tissues. By RT-PCR, Tortorella et al. (1999) observed upregulation of the aggrecanase-1 message in stimulated human fetal chondrocytes and in joint tissues from adjuvant arthritic rats. Using a GeneBridge 4 radiation hybrid panel, Ishikawa et al. (1998) mapped the ADAMTS4 gene to chromosome 1. Hurskainen et al. (1999) mapped the human ADAMTS4 gene to chromosome 1 by somatic cell hybrid analysis. They mapped the mouse Adamts4 gene to chromosome 1.

[31395] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31396] Tortorella, M. D.; Burn, T. C.; Pratta, M. A.; Abbaszade, I.; Hollis, J. M.; Liu, R.; Rosenfeld, S. A.; Copeland, R. A.; De-

cicco, C. P.; Wynn, R.; Rockwell, A.; Yang, F.; and 16 others : Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins. Science 284: 1664-1666, 1999. ; and

[31397] Hurskainen, T. L.; Hirohata, S.; Seldin, M. F.; Apte, S. S. : ADAM-TS5, ADAM-TS6, and ADAM-TS7, novel members of a new family of zinc metalloproteases: general features and genomic dist.

[31398] Further studies establishing the function and utilities of ADAMTS4 are found in John Hopkins OMIM database record ID 603876, and in cited publications numbered 760 and 8473-7606 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Ankyrin 1, Erythrocytic (ANK1, Accession XM\_016774) is another VGAM809 host target gene. ANK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ANK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANK1 BINDING SITE, designated SEQ ID:30283, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31399] Another function of VGAM809 is therefore inhibition of Ankyrin 1, Erythrocytic (ANK1, Accession XM\_016774). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANK1. Methyl-CpG Binding Domain Protein 3 (MBD3, Accession NM\_003926) is another VGAM809 host target gene. MBD3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MBD3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MBD3 BINDING SITE, designated SEQ ID:10021, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31400] Another function of VGAM809 is therefore inhibition of Methyl-CpG Binding Domain Protein 3 (MBD3, Accession NM\_003926), a gene which are subunits of the NURD (nucleosome remodeling and histone deacetylase) complex. Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBD3. The function of MBD3 and its association with various diseases and clinical conditions,

has been established by previous studies, as described hereinabove with reference to VGAM247. Spleen Focus Forming Virus (SFFV) Proviral Integration Oncogene Spi1 (SPI1, Accession NM\_003120) is another VGAM809 host target gene. SPI1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SPI1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPI1 BINDING SITE, designated SEQ ID:9091, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31401] Another function of VGAM809 is therefore inhibition of Spleen Focus Forming Virus (SFFV) Proviral Integration Oncogene Spi1 (SPI1, Accession NM\_003120), a gene which act as a lymphoid-specific enhancer. Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPI1. The function of SPI1 has been established by previous studies. DeKoter and Singh (2000) used retroviral transduction of PU.1 cDNA into mutant hematopoietic progenitors to demonstrate that differing concentrations of the protein regulate the development of B lymphocytes

as compared with macrophages. A low concentration of PU.1 protein induces the B cell fate, whereas a high concentration promotes macrophage differentiation and blocks B cell development. Conversely, a transcriptionally weakened mutant protein preferentially induces B cell generation. DeKoter and Singh (2000) concluded that graded expression of a transcription factor can be used to specify distinct cell fates in the hematopoietic system. DeKoter et al. (2002) showed that hemopoietic progenitor cells lacking PU.1 failed to express interleukin-7 receptor-alpha (IL7R; 146661) transcripts. Promoter and crosslinking analyses suggested that PU.1 directly regulates IL7R transcription. Expression of IL7R in PU.1 -/- progenitors restored IL7 (OMIM Ref. No. 146660)-dependent proliferation and induced, at low frequency, the generation of pro-B cells that underwent an apparently normal differentiation program. SPIB (OMIM Ref. No. 606802) could substitute for PU.1 early in B-cell development, but it was not required. DeKoter et al. (2002) concluded that PU.1 partially controls early B-cell development by regulating the expression of IL7R.

[31402] Full details of the abovementioned studies are described in the following publications, the disclosure of which are



hereby incorporated by reference:

[31403] DeKoter, R. P.; Singh, H. : Regulation of B lymphocyte and macrophage development by graded expression of PU.1. Science 288: 1439–1441, 2000. ; and

[31404] DeKoter, R. P.; Lee, H.-J.; Singh, H. : PU.1 regulates expression of the interleukin–7 receptor in lymphoid progenitors. Immunity 16: 297–309, 2002.

[31405] Further studies establishing the function and utilities of SPI1 are found in John Hopkins OMIM database record ID 165170, and in cited publications numbered 5127–513 and 2385 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ13841 (Accession NM\_024702) is another VGAM809 host target gene. FLJ13841 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ13841, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13841 BINDING SITE, designated SEQ ID:24016, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31406] Another function of VGAM809 is therefore inhibition of

FLJ13841 (Accession NM\_024702). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13841. FLJ20200 (Accession NM\_017708) is another VGAM809 host target gene. FLJ20200 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20200, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20200 BINDING SITE, designated SEQ ID:19287, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31407] Another function of VGAM809 is therefore inhibition of FLJ20200 (Accession NM\_017708). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20200. GMPPB (Accession NM\_021971) is another VGAM809 host target gene. GMPPB BINDING SITE1 and GMPPB BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GMPPB, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of GMPPB BINDING SITE1 and GMPPB BINDING SITE2, designated SEQ ID:22499 and SEQ ID:14981 respectively, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31408] Another function of VGAM809 is therefore inhibition of GMPPB (Accession NM\_021971). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GMPPB. Protein Phosphatase 1, Regulatory (inhibitor) Subunit 3B (PPP1R3B, Accession NM\_024607) is another VGAM809 host target gene. PPP1R3B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1R3B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R3B BINDING SITE, designated SEQ ID:23859, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31409] Another function of VGAM809 is therefore inhibition of Protein Phosphatase 1, Regulatory (inhibitor) Subunit 3B (PPP1R3B, Accession NM\_024607). Accordingly, utilities of

VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R3B. RBT1 (Accession NM\_013368) is another VGAM809 host target gene. RBT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RBT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RBT1 BINDING SITE, designated SEQ ID:15012, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31410] Another function of VGAM809 is therefore inhibition of RBT1 (Accession NM\_013368). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RBT1. Three Prime Repair Exonuclease 1 (TREX1, Accession NM\_033627) is another VGAM809 host target gene. TREX1 BINDING SITE1 and TREX1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TREX1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of TREX1 BINDING SITE1 and TREX1 BINDING SITE2, designated SEQ ID:27335 and SEQ ID:27344 respectively, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31411] Another function of VGAM809 is therefore inhibition of Three Prime Repair Exonuclease 1 (TREX1, Accession NM\_033627). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TREX1. LOC124446 (Accession XM\_058805) is another VGAM809 host target gene. LOC124446 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC124446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC124446 BINDING SITE, designated SEQ ID:36749, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31412] Another function of VGAM809 is therefore inhibition of LOC124446 (Accession XM\_058805). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC124446. LOC165229 (Accession XM\_092464) is another VGAM809 host target gene. LOC165229 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC165229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC165229 BINDING SITE, designated SEQ ID:40123, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31413] Another function of VGAM809 is therefore inhibition of LOC165229 (Accession XM\_092464). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC165229. LOC165288 (Accession XM\_092498) is another VGAM809 host target gene. LOC165288 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC165288, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC165288 BINDING SITE, designated SEQ ID:40129, to

the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31414] Another function of VGAM809 is therefore inhibition of LOC165288 (Accession XM\_092498). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC165288. LOC203871 (Accession XM\_115029) is another VGAM809 host target gene. LOC203871 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC203871, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203871 BINDING SITE, designated SEQ ID:43079, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31415] Another function of VGAM809 is therefore inhibition of LOC203871 (Accession XM\_115029). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203871. LOC253128 (Accession XM\_170726) is another VGAM809 host target gene. LOC253128 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC253128, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253128 BINDING SITE, designated SEQ ID:45486, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31416] Another function of VGAM809 is therefore inhibition of LOC253128 (Accession XM\_170726). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253128. LOC255714 (Accession XM\_172861) is another VGAM809 host target gene. LOC255714 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255714, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255714 BINDING SITE, designated SEQ ID:46140, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31417] Another function of VGAM809 is therefore inhibition of LOC255714 (Accession XM\_172861). Accordingly, utilities



of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255714. LOC51308 (Accession NM\_016606) is another VGAM809 host target gene. LOC51308 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51308, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51308 BINDING SITE, designated SEQ ID:18708, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31418] Another function of VGAM809 is therefore inhibition of LOC51308 (Accession NM\_016606). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51308. LOC90170 (Accession XM\_029589) is another VGAM809 host target gene. LOC90170 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC90170 BINDING SITE, designated SEQ ID:30910, to the nucleotide sequence of VGAM809 RNA, herein designated VGAM RNA, also designated SEQ ID:3520.

[31419] Another function of VGAM809 is therefore inhibition of LOC90170 (Accession XM\_029589). Accordingly, utilities of VGAM809 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90170. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 810 (VGAM810) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31420] VGAM810 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM810 was detected is described hereinabove with reference to Figs. 1–8.

[31421] VGAM810 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Amsacta Moorei Entomopoxvirus. VGAM810 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31422] VGAM810 gene encodes a VGAM810 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM810 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM810 precursor RNA is designated SEQ ID:796, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:796 is located at position 84714 relative to the genome of Ams-acta Moorei Entomopoxvirus.

[31423] VGAM810 precursor RNA folds onto itself, forming VGAM810 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31424] An enzyme complex designated DICER COMPLEX, `dices` the VGAM810 folded precursor RNA into VGAM810 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 51%) nucleotide sequence of VGAM810 RNA is designated SEQ ID:3521, and is provided hereinbelow with reference to the sequence listing part.

[31425] VGAM810 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM810 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM810 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[31426] VGAM810 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM810 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM810 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM810 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM810 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31427] The complementary binding of VGAM810 RNA, herein designated VGAM RNA, to host target binding sites on VGAM810 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM810 host target RNA into VGAM810 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31428] It is appreciated that VGAM810 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM810 host target genes. The mRNA of each one of this plurality of VGAM810 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM810 RNA, herein designated VGAM RNA, and which when bound by VGAM810 RNA causes inhibition of translation of respective one or more VGAM810 host target proteins.

[31429] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM810 gene, herein designated VGAM GENE, on one or more VGAM810 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[31430] It is yet further appreciated that a function of VGAM810 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of viral infection by Amsacta Moorei Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM810 correlate with, and may be deduced from, the identity of the host target genes which VGAM810 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31431] Nucleotide sequences of the VGAM810 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM810 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM810 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM810 are further described hereinbelow with reference to Table 1.

[31432] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM810 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM810 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31433] As mentioned hereinabove with reference to Fig. 1, a function of VGAM810 gene, herein designated VGAM is inhibition of expression of VGAM810 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM810 correlate with, and may be deduced from, the identity of the target genes which VGAM810 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31434] Aquaporin 9 (AQP9, Accession NM\_020980) is a VGAM810 host target gene. AQP9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AQP9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AQP9 BINDING SITE, designated SEQ ID:21969, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31435] A function of VGAM810 is therefore inhibition of Aqua-



porin 9 (AQP9, Accession NM\_020980). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AQP9. CED-6 (Accession NM\_016315) is another VGAM810 host target gene. CED-6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CED-6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CED-6 BINDING SITE, designated SEQ ID:18430, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31436] Another function of VGAM810 is therefore inhibition of CED-6 (Accession NM\_016315). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CED-6. EPLIN (Accession NM\_016357) is another VGAM810 host target gene. EPLIN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPLIN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of EPLIN BINDING SITE, designated SEQ ID:18496, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31437] Another function of VGAM810 is therefore inhibition of EPLIN (Accession NM\_016357). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPLIN. FLJ11827 (Accession NM\_025093) is another VGAM810 host target gene. FLJ11827 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11827, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11827 BINDING SITE, designated SEQ ID:24725, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31438] Another function of VGAM810 is therefore inhibition of FLJ11827 (Accession NM\_025093). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11827. KIAA0820 (Accession XM\_044463) is another VGAM810

host target gene. KIAA0820 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0820, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0820 BINDING SITE, designated SEQ ID:34220, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31439] Another function of VGAM810 is therefore inhibition of KIAA0820 (Accession XM\_044463). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0820. LOC116228 (Accession XM\_057659) is another VGAM810 host target gene. LOC116228 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC116228, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC116228 BINDING SITE, designated SEQ ID:36532, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31440] Another function of VGAM810 is therefore inhibition of LOC116228 (Accession XM\_057659). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116228. LOC120856 (Accession XM\_058509) is another VGAM810 host target gene. LOC120856 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120856, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120856 BINDING SITE, designated SEQ ID:36641, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31441] Another function of VGAM810 is therefore inhibition of LOC120856 (Accession XM\_058509). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120856. LOC149711 (Accession XM\_097720) is another VGAM810 host target gene. LOC149711 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149711, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149711 BINDING SITE, designated SEQ ID:41068, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31442] Another function of VGAM810 is therefore inhibition of LOC149711 (Accession XM\_097720). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149711. LOC163782 (Accession XM\_089138) is another VGAM810 host target gene. LOC163782 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163782, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163782 BINDING SITE, designated SEQ ID:39964, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31443] Another function of VGAM810 is therefore inhibition of LOC163782 (Accession XM\_089138). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC163782. LOC199675 (Accession XM\_113982) is another VGAM810 host target gene. LOC199675 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199675, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199675 BINDING SITE, designated SEQ ID:42586, to the nucleotide sequence of VGAM810 RNA, herein designated VGAM RNA, also designated SEQ ID:3521.

[31444] Another function of VGAM810 is therefore inhibition of LOC199675 (Accession XM\_113982). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199675. LOC253613 (Accession XM\_171225) is another VGAM810 host target gene. LOC253613 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253613, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253613 BINDING SITE, designated SEQ ID:46012, to the nucleotide sequence of VGAM810 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3521.

[31445] Another function of VGAM810 is therefore inhibition of LOC253613 (Accession XM\_171225). Accordingly, utilities of VGAM810 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253613. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 811 (VGAM811) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31446] VGAM811 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM811 was detected is described hereinabove with reference to Figs. 1–8.

[31447] VGAM811 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Melanoplus Sanguinipes Entomopoxvirus. VGAM811 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31448] VGAM811 gene encodes a VGAM811 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM811 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM811 precursor RNA is designated SEQ ID:797, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:797 is located at position 161607 relative to the genome of *Melanoplus Sanguinipes* Entomopoxvirus.

[31449] VGAM811 precursor RNA folds onto itself, forming VGAM811 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31450] An enzyme complex designated DICER COMPLEX, `dices` the VGAM811 folded precursor RNA into VGAM811 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex



comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM811 RNA is designated SEQ ID:3522, and is provided hereinbelow with reference to the sequence listing part.

[31451] VGAM811 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM811 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM811 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[31452] VGAM811 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM811 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM811 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM811 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM811 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31453] The complementary binding of VGAM811 RNA, herein designated VGAM RNA, to host target binding sites on VGAM811 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM811 host target RNA into VGAM811 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31454] It is appreciated that VGAM811 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM811 host target genes. The mRNA of

each one of this plurality of VGAM811 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM811 RNA, herein designated VGAM RNA, and which when bound by VGAM811 RNA causes inhibition of translation of respective one or more VGAM811 host target proteins.

[31455] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM811 gene, herein designated VGAM GENE, on one or more VGAM811 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[31456] It is yet further appreciated that a function of VGAM811 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of viral infection by Melanoplus Sanguinipes Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM811 correlate with, and may be deduced from, the identity of the host target genes which VGAM811 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31457] Nucleotide sequences of the VGAM811 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM811 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM811 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM811 are further described hereinbelow with reference to Table 1.

[31458] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM811 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM811 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[31459] As mentioned hereinabove with reference to Fig. 1, a function of VGAM811 gene, herein designated VGAM is inhibition of expression of VGAM811 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM811 correlate with, and may be deduced from, the identity of the target genes which VGAM811 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31460] Forkhead Box D2 (FOXD2, Accession NM\_004474) is a VGAM811 host target gene. FOXD2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FOXD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOXD2 BINDING SITE, designated SEQ ID:10786, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31461] A function of VGAM811 is therefore inhibition of Forkhead Box D2 (FOXD2, Accession NM\_004474). Accordingly, utilities of VGAM811 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with FOXD2. Lumican (LUM, Accession NM\_002345) is another VGAM811 host target gene. LUM BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LUM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LUM BINDING SITE, designated SEQ ID:8144, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31462] Another function of VGAM811 is therefore inhibition of Lumican (LUM, Accession NM\_002345). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LUM. Ubiquitin-conjugating Enzyme E2H (UBC8 homolog, yeast) (UBE2H, Accession NM\_003344) is another VGAM811 host target gene. UBE2H BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by UBE2H, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2H BINDING SITE,

designated SEQ ID:9351, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31463] Another function of VGAM811 is therefore inhibition of Ubiquitin-conjugating Enzyme E2H (UBC8 homolog, yeast) (UBE2H, Accession NM\_003344), a gene which catalyzes the covalent attachment of ubiquitin to other proteins. Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2H. The function of UBE2H has been established by previous studies. Ubiquitin-conjugating enzymes catalyze the covalent attachment of ubiquitin to cellular substrates. Kaiser et al. (1994) isolated a novel ubiquitin-conjugating enzyme from human placenta and cloned the corresponding cDNA. DNA sequencing revealed that this gene, symbolized UBCH2 by them, encodes a protein with significant sequence similarity to yeast UBC8. They discovered that yeast UBC8 is interrupted by a single intron bearing an unusual branch point sequence. The authors noted that yeast UBC8 exhibited 54% amino acid sequence identity to human UBCH2. Moreover, full-length yeast and human enzymes expressed from the cDNAs showed similar enzymatic activities in vitro by catalyzing

the ubiquitination of histones, suggesting that the 2 enzymes may fulfill similar functions in vivo. By study of hamster/human hybrid cell DNAs, Kaiser et al. (1994) demonstrated that the human UBC8 gene is located on chromosome 7. Hayashida et al. (2000) constructed a 1-Mb physical and transcript map of 7q32 and mapped UBE2H to a region between D7S530 and D7S649.

[31464] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31465] Hayashida, S.; Yamasaki, K.; Asada, Y.; Soeda, E.; Niikawa, N.; Kishino, T. : Construction of a physical and transcript map flanking the imprinted MEST/PEG1 region at 7q32. Genomics 66: 221–225, 2000. ; and

[31466] Kaiser, P.; Seufert, W.; Hofferer, L.; Kofler, B.; Sachsenmaier, C.; Herzog, H.; Jentsch, S.; Schweiger, M.; Schneider, R. : Human ubiquitin-conjugating enzyme homologous to yeast UBC8.

[31467] Further studies establishing the function and utilities of UBE2H are found in John Hopkins OMIM database record ID 601082, and in cited publications numbered 9924 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 6



Open Reading Frame 37 (C6orf37, Accession XM\_041375) is another VGAM811 host target gene. C6orf37 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C6orf37, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C6orf37 BINDING SITE, designated SEQ ID:33507, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31468] Another function of VGAM811 is therefore inhibition of Chromosome 6 Open Reading Frame 37 (C6orf37, Accession XM\_041375). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C6orf37. C6orf5 (Accession NM\_015524) is another VGAM811 host target gene. C6orf5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C6orf5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C6orf5 BINDING SITE, designated SEQ ID:17778, to the nucleotide sequence of VGAM811 RNA,

herein designated VGAM RNA, also designated SEQ ID:3522.

[31469] Another function of VGAM811 is therefore inhibition of C6orf5 (Accession NM\_015524). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C6orf5. DREV1 (Accession NM\_016025) is another VGAM811 host target gene. DREV1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DREV1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DREV1 BINDING SITE, designated SEQ ID:18105, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31470] Another function of VGAM811 is therefore inhibition of DREV1 (Accession NM\_016025). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DREV1. FLJ12716 (Accession NM\_021942) is another VGAM811 host target gene. FLJ12716 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ12716, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12716 BINDING SITE, designated SEQ ID:22457, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31471] Another function of VGAM811 is therefore inhibition of FLJ12716 (Accession NM\_021942). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12716. FLJ13920 (Accession NM\_024558) is another VGAM811 host target gene. FLJ13920 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13920, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13920 BINDING SITE, designated SEQ ID:23780, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31472] Another function of VGAM811 is therefore inhibition of FLJ13920 (Accession NM\_024558). Accordingly, utilities of

VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13920. FLJ23071 (Accession NM\_025192) is another VGAM811 host target gene. FLJ23071 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23071, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23071 BINDING SITE, designated SEQ ID:24845, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31473] Another function of VGAM811 is therefore inhibition of FLJ23071 (Accession NM\_025192). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23071. FLJ23119 (Accession NM\_024652) is another VGAM811 host target gene. FLJ23119 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ23119, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23119 BINDING SITE,

designated SEQ ID:23948, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31474] Another function of VGAM811 is therefore inhibition of FLJ23119 (Accession NM\_024652). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23119. KIAA1500 (Accession XM\_034353) is another VGAM811 host target gene. KIAA1500 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1500 BINDING SITE, designated SEQ ID:32067, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31475] Another function of VGAM811 is therefore inhibition of KIAA1500 (Accession XM\_034353). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1500. KIAA1615 (Accession XM\_044021) is another VGAM811 host target gene. KIAA1615 BINDING SITE is

HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1615, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1615 BINDING SITE, designated SEQ ID:34079, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31476] Another function of VGAM811 is therefore inhibition of KIAA1615 (Accession XM\_044021). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1615. SRB7 Suppressor of RNA Polymerase B Homolog (yeast) (SURB7, Accession NM\_004264) is another VGAM811 host target gene. SURB7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SURB7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SURB7 BINDING SITE, designated SEQ ID:10464, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31477] Another function of VGAM811 is therefore inhibition of SRB7 Suppressor of RNA Polymerase B Homolog (yeast) (SURB7, Accession NM\_004264). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SURB7. LOC122792 (Accession NM\_145251) is another VGAM811 host target gene. LOC122792 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC122792, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC122792 BINDING SITE, designated SEQ ID:29761, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31478] Another function of VGAM811 is therefore inhibition of LOC122792 (Accession NM\_145251). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC122792. LOC127435 (Accession XM\_072088) is another VGAM811 host target gene. LOC127435 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC127435, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127435 BINDING SITE, designated SEQ ID:37462, to the nucleotide sequence of VGAM811 RNA, herein designated VGAM RNA, also designated SEQ ID:3522.

[31479] Another function of VGAM811 is therefore inhibition of LOC127435 (Accession XM\_072088). Accordingly, utilities of VGAM811 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127435. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 812 (VGAM812) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31480] VGAM812 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM812 was detected is described hereinabove with reference to Figs. 1-8.

[31481] VGAM812 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4.



VGAM812 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31482] VGAM812 gene encodes a VGAM812 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM812 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM812 precursor RNA is designated SEQ ID:798, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:798 is located at position 60284 relative to the genome of Murid Herpesvirus 4.

[31483] VGAM812 precursor RNA folds onto itself, forming VGAM812 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31484] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM812 folded precursor RNA into VGAM812 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM812 RNA is designated SEQ ID:3523, and is provided hereinbelow with reference to the sequence listing part.

[31485] VGAM812 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM812 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM812 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31486] VGAM812 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM812 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM812 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM812 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM812 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31487] The complementary binding of VGAM812 RNA, herein designated VGAM RNA, to host target binding sites on VGAM812 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM812 host target RNA into VGAM812 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31488] It is appreciated that VGAM812 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM812 host target genes. The mRNA of each one of this plurality of VGAM812 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM812 RNA, herein designated VGAM RNA, and which when bound by VGAM812 RNA causes inhibition of translation of respective one or more VGAM812 host target proteins.

[31489] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM812 gene, herein designated VGAM GENE, on one or more VGAM812 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31490] It is yet further appreciated that a function of VGAM812 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM812 correlate with, and may be deduced from, the identity of the host target genes which VGAM812 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31491] Nucleotide sequences of the VGAM812 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM812 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM812 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM812 are further described hereinbelow with reference to Table 1.

[31492] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM812 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM812 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31493] As mentioned hereinabove with reference to Fig. 1, a function of VGAM812 gene, herein designated VGAM is inhibition of expression of VGAM812 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM812 correlate with, and may be deduced from, the identity of the target genes which VGAM812 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31494] DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide, Y Chromosome (DBY, Accession NM\_004660) is a VGAM812 host target gene. DBY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DBY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DBY BINDING SITE, designated SEQ

ID:11030, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31495] A function of VGAM812 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide, Y Chromosome (DBY, Accession NM\_004660), a gene which plays a key role in the spermatogenic process. Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DBY. The function of DBY and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM374.Laminin, Gamma 1 (formerly LAMB2) (LAMC1, Accession NM\_002293) is another VGAM812 host target gene. LAMC1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LAMC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LAMC1 BINDING SITE, designated SEQ ID:8080, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31496] Another function of VGAM812 is therefore inhibition of Laminin, Gamma 1 (formerly LAMB2) (LAMC1, Accession NM\_002293), a gene which may mediate the attachment, migration, and organization of cells into tissues. Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LAMC1. The function of LAMC1 has been established by previous studies. Laminin is a heterotrimeric extracellular matrix protein consisting of 3 chains: alpha (LAMA1; 150320), beta (LAMB1; 150240), and gamma (formerly A, B1, and B2, respectively). Several isoforms of each chain have been identified. Laminin gamma-1 is the most ubiquitously expressed laminin subunit (Burgeson et al., 1994; Miner et al., 1997). In mouse, the laminin subunits alpha-1, beta-1, and gamma-1 are expressed in the preimplantation embryo before the appearance of the first basement membrane of the trophectodermal epithelium. Smyth et al. (1999) targeted the LAMC1 gene by homologous recombination in mouse embryonic stem (ES) cells. Mice heterozygous for the mutation had a normal phenotype and were fertile, whereas homozygous mutant embryos did not survive beyond day 5.5 postcoitum. These embryos lacked basement membranes, and although the



blastocysts had expanded, primitive endoderm cells remained in the inner mass, and the parietal yolk sac did not develop. Cultured ES cells appeared normal after targeting both LAMC1 genes, but the embryoid bodies derived from them also lacked basement membranes, having disorganized extracellular deposits of the basement membrane proteins collagen IV and perlecan, and the cells failed to differentiate into stable myotubes. Nomenclature: Burgeson et al. (1994), a group of 14 leading researchers in the field of connective tissue proteins, adopted a new nomenclature for the laminins. They were numbered with arabic numerals in the order discovered. The previous A, B1, and B2 chains, and their isoforms, are alpha, beta, and gamma, respectively, followed by an arabic numeral to identify the isoform. For example, the first laminin identified from the Engelbreth-Holm-Swarm tumor (EHS) was designated laminin-1 with the chain composition alpha-1/beta-1/gamma-1. The genes for these 3 chains are LAMA1, LAMB1 (OMIM Ref. No. 150240), and LAMC1.

[31497] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31498] Smyth, N.; Vatansever, H. S.; Murray, P.; Meyer, M.; Frie,

C.; Paulsson, M.; Edgar, D. : Absence of basement membranes after targeting the LAMC1 gene results in embryonic lethality due to failure of endoderm differentiation. J. Cell Biol. 144: 151–160, 1999. ; and

[31499] Burgeson, R. E.; Chiquet, M.; Deutzmann, R.; Ekblom, P.; Engel, J.; Kleinman, H.; Martin, G. R.; Meneguzzi, G.; Paulsson, M.; Sanes, J.; Timpl, R.; Tryggvason, K.; Yamada, Y.; Yurchenco.

[31500] Further studies establishing the function and utilities of LAMC1 are found in John Hopkins OMIM database record ID 150290, and in cited publications numbered 11982–306 and 3913–3472 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA1941 (Accession XM\_059318) is another VGAM812 host target gene. KIAA1941 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1941, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1941 BINDING SITE, designated SEQ ID:36953, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31501] Another function of VGAM812 is therefore inhibition of KIAA1941 (Accession XM\_059318). Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1941. RAB39, Member RAS Oncogene Family (RAB39, Accession XM\_084662) is another VGAM812 host target gene. RAB39 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB39, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB39 BINDING SITE, designated SEQ ID:37648, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31502] Another function of VGAM812 is therefore inhibition of RAB39, Member RAS Oncogene Family (RAB39, Accession XM\_084662). Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB39. SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily F, Member 1 (SMARCF1, Accession NM\_006015) is another VGAM812 host target gene.

SMARCF1 BINDING SITE1 through SMARCF1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SMARCF1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMARCF1 BINDING SITE1 through SMARCF1 BINDING SITE3, designated SEQ ID:12627, SEQ ID:20525 and SEQ ID:29165 respectively, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31503] Another function of VGAM812 is therefore inhibition of SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily F, Member 1 (SMARCF1, Accession NM\_006015). Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMARCF1. TUSP (Accession NM\_020245) is another VGAM812 host target gene. TUSP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TUSP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of TUSP BINDING SITE, designated SEQ ID:21526, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31504] Another function of VGAM812 is therefore inhibition of TUSP (Accession NM\_020245). Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TUSP. LOC149420 (Accession XM\_086530) is another VGAM812 host target gene. LOC149420 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149420 BINDING SITE, designated SEQ ID:38749, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31505] Another function of VGAM812 is therefore inhibition of LOC149420 (Accession XM\_086530). Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149420. LOC90786 (Accession XM\_034127) is an-

other VGAM812 host target gene. LOC90786 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90786, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90786 BINDING SITE, designated SEQ ID:32014, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31506] Another function of VGAM812 is therefore inhibition of LOC90786 (Accession XM\_034127). Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90786. LOC91661 (Accession NM\_138372) is another VGAM812 host target gene. LOC91661 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91661, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91661 BINDING SITE, designated SEQ ID:28751, to the nucleotide sequence of VGAM812 RNA, herein designated VGAM RNA, also designated SEQ ID:3523.

[31507] Another function of VGAM812 is therefore inhibition of LOC91661 (Accession NM\_138372). Accordingly, utilities of VGAM812 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91661. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 813 (VGAM813) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31508] VGAM813 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM813 was detected is described hereinabove with reference to Figs. 1–8.

[31509] VGAM813 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM813 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31510] VGAM813 gene encodes a VGAM813 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM813

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM813 precursor RNA is designated SEQ ID:799, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:799 is located at position 61060 relative to the genome of Murid Herpesvirus 4.

[31511] VGAM813 precursor RNA folds onto itself, forming VGAM813 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31512] An enzyme complex designated DICER COMPLEX, `dices` the VGAM813 folded precursor RNA into VGAM813 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other



necessary proteins. A probable (over 55%) nucleotide sequence of VGAM813 RNA is designated SEQ ID:3524, and is provided hereinbelow with reference to the sequence listing part.

[31513] VGAM813 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM813 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM813 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31514] VGAM813 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM813 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM813 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM813 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM813 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31515] The complementary binding of VGAM813 RNA, herein designated VGAM RNA, to host target binding sites on VGAM813 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM813 host target RNA into VGAM813 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31516] It is appreciated that VGAM813 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM813 host target genes. The mRNA of each one of this plurality of VGAM813 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM813 RNA, herein designated VGAM RNA, and which when bound by VGAM813 RNA causes inhibition of translation of respective one or more VGAM813 host target proteins.

[31517] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM813 gene, herein designated VGAM GENE, on one or more VGAM813 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31518] It is yet further appreciated that a function of VGAM813 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM813 correlate with, and may be deduced from, the identity of the host target genes which VGAM813 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31519] Nucleotide sequences of the VGAM813 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM813 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM813 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM813 are further described hereinbelow with reference to Table 1.

[31520] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM813 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM813 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[31521] As mentioned hereinabove with reference to Fig. 1, a function of VGAM813 gene, herein designated VGAM is inhibition of expression of VGAM813 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM813 correlate with, and may be deduced from, the identity of the target genes which VGAM813 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31522] Bromodomain Adjacent to Zinc Finger Domain, 2B (BAZ2B, Accession NM\_013450) is a VGAM813 host target gene. BAZ2B BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BAZ2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BAZ2B BINDING SITE, designated SEQ ID:15123, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31523] A function of VGAM813 is therefore inhibition of Bromodomain Adjacent to Zinc Finger Domain, 2B (BAZ2B, Accession NM\_013450). Accordingly, utilities of VGAM813 in-

clude diagnosis, prevention and treatment of diseases and clinical conditions associated with BAZ2B. CAMP Responsive Element Binding Protein-like 2 (CREBL2, Accession NM\_001310) is another VGAM813 host target gene.

CREBL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CREBL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CREBL2 BINDING SITE, designated SEQ ID:6994, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31524] Another function of VGAM813 is therefore inhibition of CAMP Responsive Element Binding Protein-like 2 (CREBL2, Accession NM\_001310). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CREBL2. Fibronectin Leucine Rich Transmembrane Protein 2 (FLRT2, Accession NM\_013231) is another VGAM813 host target gene. FLRT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLRT2, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLRT2 BINDING SITE, designated SEQ ID:14873, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31525] Another function of VGAM813 is therefore inhibition of Fibronectin Leucine Rich Transmembrane Protein 2 (FLRT2, Accession NM\_013231), a gene which may have a function in cell adhesion and/or receptor signaling. Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLRT2. The function of FLRT2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. Chemokine (C-C motif) Receptor 6 (CCR6, Accession NM\_004367) is another VGAM813 host target gene. CCR6 BINDING SITE1 and CCR6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CCR6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CCR6

BINDING SITE1 and CCR6 BINDING SITE2, designated SEQ ID:10574 and SEQ ID:25366 respectively, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31526] Another function of VGAM813 is therefore inhibition of Chemokine (C-C motif) Receptor 6 (CCR6, Accession NM\_004367). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CCR6. Heat Shock 90kDa Protein 1, Alpha-like 3 (HSPCAL3, Accession XM\_084514) is another VGAM813 host target gene. HSPCAL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPCAL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPCAL3 BINDING SITE, designated SEQ ID:37619, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31527] Another function of VGAM813 is therefore inhibition of Heat Shock 90kDa Protein 1, Alpha-like 3 (HSPCAL3, Accession XM\_084514). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases



and clinical conditions associated with HSPCAL3.

KIAA1529 (Accession XM\_047336) is another VGAM813 host target gene. KIAA1529 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1529, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1529 BINDING SITE, designated SEQ ID:34950, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31528] Another function of VGAM813 is therefore inhibition of KIAA1529 (Accession XM\_047336). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1529. Phorbol-12-myristate-13-acetate-induced Protein 1 (PMAIP1, Accession NM\_021127) is another VGAM813 host target gene. PMAIP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PMAIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PMAIP1 BINDING

SITE, designated SEQ ID:22101, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31529] Another function of VGAM813 is therefore inhibition of Phorbol-12-myristate-13-acetate-induced Protein 1 (PMAIP1, Accession NM\_021127). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PMAIP1. LOC162333 (Accession XM\_102591) is another VGAM813 host target gene. LOC162333 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC162333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162333 BINDING SITE, designated SEQ ID:42118, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31530] Another function of VGAM813 is therefore inhibition of LOC162333 (Accession XM\_102591). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162333. LOC169270 (Accession XM\_095607) is an-

other VGAM813 host target gene. LOC169270 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC169270, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169270 BINDING SITE, designated SEQ ID:40273, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31531] Another function of VGAM813 is therefore inhibition of LOC169270 (Accession XM\_095607). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC169270. LOC220763 (Accession XM\_055551) is another VGAM813 host target gene. LOC220763 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220763, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220763 BINDING SITE, designated SEQ ID:36302, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31532] Another function of VGAM813 is therefore inhibition of LOC220763 (Accession XM\_055551). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220763. LOC51277 (Accession XM\_087054) is another VGAM813 host target gene. LOC51277 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51277, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51277 BINDING SITE, designated SEQ ID:39022, to the nucleotide sequence of VGAM813 RNA, herein designated VGAM RNA, also designated SEQ ID:3524.

[31533] Another function of VGAM813 is therefore inhibition of LOC51277 (Accession XM\_087054). Accordingly, utilities of VGAM813 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51277. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 814 (VGAM814) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[31534] VGAM814 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM814 was detected is described hereinabove with reference to Figs. 1–8.

[31535] VGAM814 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Murid Herpesvirus 4. VGAM814 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31536] VGAM814 gene encodes a VGAM814 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM814 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM814 precursor RNA is designated SEQ ID:800, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:800 is located at position 58920 relative to the genome of Murid Herpesvirus 4.

[31537] VGAM814 precursor RNA folds onto itself, forming VGAM814 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[31538] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM814 folded precursor RNA into VGAM814 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 76%) nucleotide se-  
quence of VGAM814 RNA is designated SEQ ID:3525, and  
is provided hereinbelow with reference to the sequence  
listing part.

[31539] VGAM814 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM814 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM814 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31540] VGAM814 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM814 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM814 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM814 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM814 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31541] The complementary binding of VGAM814 RNA, herein designated VGAM RNA, to host target binding sites on VGAM814 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM814 host target RNA into VGAM814 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31542] It is appreciated that VGAM814 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM814 host target genes. The mRNA of each one of this plurality of VGAM814 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM814 RNA, herein designated VGAM RNA, and which when bound by VGAM814 RNA causes inhibition of translation of respective one or more VGAM814 host target proteins.

[31543] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by



VGAM814 gene, herein designated VGAM GENE, on one or more VGAM814 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31544] It is yet further appreciated that a function of VGAM814 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of viral infection by Murid Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM814 correlate with, and may be deduced from, the identity of the host target genes which VGAM814 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

- [31545] Nucleotide sequences of the VGAM814 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM814 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM814 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM814 are further described hereinbelow with reference to Table 1.
- [31546] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM814 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM814 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [31547] As mentioned hereinabove with reference to Fig. 1, a function of VGAM814 gene, herein designated VGAM is inhibition of expression of VGAM814 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM814 correlate with, and may be deduced from, the identity of the target genes which VGAM814 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31548] FK506 Binding Protein 1A, 12kDa (FKBP1A, Accession NM\_000801) is a VGAM814 host target gene. FKBP1A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FKBP1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FKBP1A BINDING SITE, designated SEQ ID:6473, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31549] A function of VGAM814 is therefore inhibition of FK506 Binding Protein 1A, 12kDa (FKBP1A, Accession NM\_000801), a gene which FK506-binding protein 1A. Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FKBP1A. The function of FKBP1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM57. Follistatin-like 3 (secreted glycoprotein) (FSTL3, Accession NM\_005860) is another VGAM814 host target gene. FSTL3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FSTL3, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FSTL3 BINDING SITE, designated SEQ ID:12467, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31550] Another function of VGAM814 is therefore inhibition of Follistatin-like 3 (secreted glycoprotein) (FSTL3, Accession NM\_005860), a gene which is a member of the follistatin-module-protein family. Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FSTL3. The function of FSTL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200.CGI-142 (Accession NM\_016073) is another VGAM814 host target gene. CGI-142 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CGI-142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CGI-142 BINDING SITE, designated SEQ ID:18146, to the nucleotide

sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31551] Another function of VGAM814 is therefore inhibition of CGI-142 (Accession NM\_016073). Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CGI-142. FLJ21777 (Accession NM\_032209) is another VGAM814 host target gene. FLJ21777 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21777, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21777 BINDING SITE, designated SEQ ID:25922, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31552] Another function of VGAM814 is therefore inhibition of FLJ21777 (Accession NM\_032209). Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21777. IMP13 (Accession NM\_014652) is another VGAM814 host target gene. IMP13 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded

by IMP13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IMP13 BINDING SITE, designated SEQ ID:16074, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31553] Another function of VGAM814 is therefore inhibition of IMP13 (Accession NM\_014652). Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IMP13. KIAA1671 (Accession XM\_037809) is another VGAM814 host target gene. KIAA1671 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1671, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1671 BINDING SITE, designated SEQ ID:32692, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31554] Another function of VGAM814 is therefore inhibition of KIAA1671 (Accession XM\_037809). Accordingly, utilities

of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1671. PPI5PIV (Accession NM\_019892) is another VGAM814 host target gene. PPI5PIV BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPI5PIV, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPI5PIV BINDING SITE, designated SEQ ID:21274, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31555] Another function of VGAM814 is therefore inhibition of PPI5PIV (Accession NM\_019892). Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPI5PIV. STATI2 (Accession NM\_003877) is another VGAM814 host target gene. STATI2 BINDING SITE1 and STATI2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by STATI2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STATI2

BINDING SITE1 and STATI2 BINDING SITE2, designated SEQ ID:9958 and SEQ ID:45369 respectively, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31556] Another function of VGAM814 is therefore inhibition of STATI2 (Accession NM\_003877). Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STATI2. LOC201685 (Accession XM\_117325) is another VGAM814 host target gene. LOC201685 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC201685, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201685 BINDING SITE, designated SEQ ID:43388, to the nucleotide sequence of VGAM814 RNA, herein designated VGAM RNA, also designated SEQ ID:3525.

[31557] Another function of VGAM814 is therefore inhibition of LOC201685 (Accession XM\_117325). Accordingly, utilities of VGAM814 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201685. Fig. 1 further provides a conceptual descrip-



tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 815 (VGAM815) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31558] VGAM815 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM815 was detected is described hereinabove with reference to Figs. 1–8.

[31559] VGAM815 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Macaca Mulatta Rhadinovirus. VGAM815 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31560] VGAM815 gene encodes a VGAM815 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM815 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM815 precursor RNA is designated SEQ ID:801, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:801 is

located at position 59708 relative to the genome of Macaca Mulatta Rhadinovirus.

[31561] VGAM815 precursor RNA folds onto itself, forming VGAM815 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31562] An enzyme complex designated DICER COMPLEX, `dices` the VGAM815 folded precursor RNA into VGAM815 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 52%) nucleotide sequence of VGAM815 RNA is designated SEQ ID:3526, and is provided hereinbelow with reference to the sequence listing part.

[31563] VGAM815 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM815 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM815 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[31564] VGAM815 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM815 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM815 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM815 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM815 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[31565] The complementary binding of VGAM815 RNA, herein designated VGAM RNA, to host target binding sites on VGAM815 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM815 host target RNA into VGAM815 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31566] It is appreciated that VGAM815 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM815 host target genes. The mRNA of each one of this plurality of VGAM815 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM815 RNA, herein designated VGAM RNA, and which when bound by VGAM815 RNA causes inhibition of translation of respective one or more VGAM815

host target proteins.

[31567] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM815 gene, herein designated VGAM GENE, on one or more VGAM815 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31568] It is yet further appreciated that a function of VGAM815 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM815 include diagnosis, prevention and treatment of viral infection by Macaca Mulatta Rhadi-

novirus. Specific functions, and accordingly utilities, of VGAM815 correlate with, and may be deduced from, the identity of the host target genes which VGAM815 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31569] Nucleotide sequences of the VGAM815 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM815 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM815 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM815 are further described hereinbelow with reference to Table 1.

[31570] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM815 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM815 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31571] As mentioned hereinabove with reference to Fig. 1, a function of VGAM815 gene, herein designated VGAM is inhibition of expression of VGAM815 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM815 correlate with, and may be deduced from, the identity of the target genes which VGAM815 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31572] KIAA0089 (Accession XM\_046056) is a VGAM815 host target gene. KIAA0089 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0089, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0089 BINDING SITE, designated SEQ ID:34663, to the nucleotide sequence of VGAM815 RNA, herein designated VGAM RNA, also designated SEQ ID:3526.

[31573] A function of VGAM815 is therefore inhibition of KIAA0089 (Accession XM\_046056). Accordingly, utilities of VGAM815 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0089. LOC197196 (Accession XM\_117003) is another VGAM815 host target gene. LOC197196 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197196, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197196 BINDING SITE, designated SEQ ID:43200, to the nucleotide sequence of VGAM815 RNA, herein designated VGAM RNA, also designated SEQ ID:3526.

[31574] Another function of VGAM815 is therefore inhibition of LOC197196 (Accession XM\_117003). Accordingly, utilities of VGAM815 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197196. LOC200982 (Accession XM\_117305) is another VGAM815 host target gene. LOC200982 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200982, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200982 BINDING SITE, designated SEQ ID:43374, to the nucleotide sequence of VGAM815 RNA, herein designated VGAM RNA, also designated SEQ ID:3526.

[31575] Another function of VGAM815 is therefore inhibition of LOC200982 (Accession XM\_117305). Accordingly, utilities of VGAM815 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC200982. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 816 (VGAM816) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31576] VGAM816 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM816 was detected is described hereinabove with reference to Figs. 1–8.

[31577] VGAM816 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Macaca Mulatta Rhadinovirus. VGAM816 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31578] VGAM816 gene encodes a VGAM816 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM816 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM816 precursor RNA is designated SEQ ID:802, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:802 is located at position 60360 relative to the genome of Macaca Mulatta Rhadinovirus.

[31579] VGAM816 precursor RNA folds onto itself, forming VGAM816 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31580] An enzyme complex designated DICER COMPLEX, `dices` the VGAM816 folded precursor RNA into VGAM816 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM816 RNA is designated SEQ ID:3527, and is provided hereinbelow with reference to the sequence listing part.

[31581] VGAM816 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM816 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM816 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31582] VGAM816 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM816 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM816 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM816 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM816 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[31583] The complementary binding of VGAM816 RNA, herein designated VGAM RNA, to host target binding sites on VGAM816 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM816 host target RNA into VGAM816 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31584] It is appreciated that VGAM816 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM816 host target genes. The mRNA of each one of this plurality of VGAM816 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM816 RNA, herein designated VGAM RNA, and which when bound by VGAM816 RNA causes in-

hibition of translation of respective one or more VGAM816 host target proteins.

[31585] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM816 gene, herein designated VGAM GENE, on one or more VGAM816 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31586] It is yet further appreciated that a function of VGAM816 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM816 include diagnosis, prevention and

treatment of viral infection by Macaca Mulatta Rhadinovirus. Specific functions, and accordingly utilities, of VGAM816 correlate with, and may be deduced from, the identity of the host target genes which VGAM816 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31587] Nucleotide sequences of the VGAM816 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM816 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM816 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM816 are further described hereinbelow with reference to Table 1.

[31588] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM816 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM816 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31589] As mentioned hereinabove with reference to Fig. 1, a function of VGAM816 gene, herein designated VGAM is inhibition of expression of VGAM816 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM816 correlate with, and may be deduced from, the identity of the target genes which VGAM816 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31590] ADP-ribosylation Factor 4-like (ARF4L, Accession XM\_045890) is a VGAM816 host target gene. ARF4L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARF4L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARF4L BINDING SITE, designated SEQ ID:34605, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31591] A function of VGAM816 is therefore inhibition of ADP-ribosylation Factor 4-like (ARF4L, Accession XM\_045890). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARF4L. Calcium Channel, Voltage-dependent, L Type, Alpha 1C Subunit (CACNA1C, Accession NM\_000719) is another VGAM816 host target gene. CACNA1C BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by CACNA1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CACNA1C BINDING SITE, designated SEQ ID:6381, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31592] Another function of VGAM816 is therefore inhibition of Calcium Channel, Voltage-dependent, L Type, Alpha 1C Subunit (CACNA1C, Accession NM\_000719), a gene which is alpha-1 subunit of DHP-sensitive calcium channels from cardiac muscle and the brain. Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CACNA1C. The function of CACNA1C and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM182. Prostaglandin F2 Receptor Negative Regulator (PTGFRN, Accession XM\_040709) is another VGAM816 host target gene. PTGFRN BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PTGFRN, corresponding to a HOST TARGET



binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTGFRN BINDING SITE, designated SEQ ID:33366, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31593] Another function of VGAM816 is therefore inhibition of Prostaglandin F2 Receptor Negative Regulator (PTGFRN, Accession XM\_040709), a gene which inhibits the binding of prostaglandin f2-alpha (pgf2- alpha) to its specific fp receptor. Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTGFRN. The function of PTGFRN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM125. RAD52 Homolog (*S. cerevisiae*) (RAD52, Accession NM\_134422) is another VGAM816 host target gene. RAD52 BINDING SITE1 through RAD52 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RAD52, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of RAD52 BINDING SITE1 through RAD52 BINDING SITE3, designated SEQ ID:28646, SEQ ID:28654 and SEQ ID:28663 respectively, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31594] Another function of VGAM816 is therefore inhibition of RAD52 Homolog (*S. cerevisiae*) (RAD52, Accession NM\_134422). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAD52. Solute Carrier Family 4, Sodium Bicarbonate Cotransporter, Member 4 (SLC4A4, Accession NM\_003759) is another VGAM816 host target gene. SLC4A4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC4A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC4A4 BINDING SITE, designated SEQ ID:9839, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31595] Another function of VGAM816 is therefore inhibition of Solute Carrier Family 4, Sodium Bicarbonate Cotrans-

porter, Member 4 (SLC4A4, Accession NM\_003759), a gene which is a sodium bicarbonate cotransporter. Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC4A4. The function of SLC4A4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM222. Serine/arginine Repetitive Matrix 1 (SRRM1, Accession NM\_005839) is another VGAM816 host target gene. SRRM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SRRM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRRM1 BINDING SITE, designated SEQ ID:12452, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31596] Another function of VGAM816 is therefore inhibition of Serine/arginine Repetitive Matrix 1 (SRRM1, Accession NM\_005839). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRRM1. Transducin

(beta)-like 2 (TBL2, Accession NM\_032988) is another VGAM816 host target gene. TBL2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TBL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TBL2 BINDING SITE, designated SEQ ID:26870, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31597] Another function of VGAM816 is therefore inhibition of Transducin (beta)-like 2 (TBL2, Accession NM\_032988), a gene which is of unknown function. Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TBL2. The function of TBL2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM229. Translocase of Inner Mitochondrial Membrane 17 Homolog A (yeast) (TIMM17A, Accession NM\_006335) is another VGAM816 host target gene. TIMM17A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by

TIMM17A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMM17A BINDING SITE, designated SEQ ID:13035, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31598] Another function of VGAM816 is therefore inhibition of Translocase of Inner Mitochondrial Membrane 17 Homolog A (yeast) (TIMM17A, Accession NM\_006335), a gene which translocates nuclear-encoded proteins into the mitochondrion. Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIMM17A. The function of TIMM17A has been established by previous studies. By searching EST databases for homologs of yeast Tim17, Bomer et al. (1996) isolated a cDNA encoding human TIMM17A. Using similar methods, Bauer et al. (1999) also cloned a TIMM17A cDNA. Sequence analysis predicted that the 171-amino acid TIMM17A protein shares 46% amino acid identity with yeast Tim17 and contains 4 hydrophobic membrane-spanning segments, conserving the N-out/C-out topology of the yeast protein. Bauer et al.

(1999) found that TIMM17A is 76% identical to TIMM17B (OMIM Ref. No. 300249), differing primarily in the C terminus. Bomer et al. (1996) determined that TIMM17A is imported into the mitochondria via the TOMM70 rather than the more common TOMM20 (OMIM Ref. No. 601848) pathway. By Northern blot analysis, Bauer et al. (1999) detected ubiquitous expression of a 1.6-kb TIMM17A transcript that is most abundant in heart and brain, weaker in skeletal muscle, followed by pancreas, placenta, kidney, and liver. Western blot analysis showed that TIMM17A colocalizes with the inner membrane fraction of mitochondria as a 17-kD protein. Individually, TIMM17A and TIMM17B interact with TIMM23 (OMIM Ref. No. 605034), forming 2 distinct 110-kD complexes.

[31599] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31600] Bomer, U.; Rassow, J.; Zufall, N.; Pfanner, N.; Meijer, M.; Maarse, A. C. : The preprotein translocase of the inner mitochondrial membrane: evolutionary conservation of targeting and assembly of Tim17. *J. Molec. Biol.* 262: 389–395, 1996. ; and

[31601] Bauer, M. F.; Gempel, K.; Reichert, A. S.; Rappold, G. A.;

Lichtner, P.; Gerbitz, K. D.; Neupert, W.; Brunner, M.; Hofmann, S. : Genetic and structural characterization of the human mito.

[31602] Further studies establishing the function and utilities of TIMM17A are found in John Hopkins OMIM database record ID 605057, and in cited publications numbered 5030–5031 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Accession NM\_003842) is another VGAM816 host target gene. TNFRSF10B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFRSF10B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFRSF10B BINDING SITE, designated SEQ ID:9941, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31603] Another function of VGAM816 is therefore inhibition of Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Accession NM\_003842), a gene which forms complex that induces apoptosis. Accordingly, utilities of

VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFRSF10B. The function of TNFRSF10B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM400. Zinc Finger Protein 205 (ZNF205, Accession NM\_003456) is another VGAM816 host target gene. ZNF205 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZNF205, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF205 BINDING SITE, designated SEQ ID:9514, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31604] Another function of VGAM816 is therefore inhibition of Zinc Finger Protein 205 (ZNF205, Accession NM\_003456). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF205. ADG-90 (Accession NM\_033069) is another VGAM816 host target gene. ADG-90 BINDING SITE is HOST TARGET binding site found in the 5' un-



translated region of mRNA encoded by ADG-90, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADG-90 BINDING SITE, designated SEQ ID:26935, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31605] Another function of VGAM816 is therefore inhibition of ADG-90 (Accession NM\_033069). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADG-90. DKFZP434H132 (Accession NM\_015492) is another VGAM816 host target gene. DKFZP434H132 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434H132, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434H132 BINDING SITE, designated SEQ ID:17762, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31606] Another function of VGAM816 is therefore inhibition of DKFZP434H132 (Accession NM\_015492). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434H132. FLJ11155 (Accession NM\_018342) is another VGAM816 host target gene. FLJ11155 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11155, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11155 BINDING SITE, designated SEQ ID:20349, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31607] Another function of VGAM816 is therefore inhibition of FLJ11155 (Accession NM\_018342). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11155. FLJ11259 (Accession NM\_018370) is another VGAM816 host target gene. FLJ11259 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11259, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11259 BINDING SITE, designated SEQ ID:20387, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31608] Another function of VGAM816 is therefore inhibition of FLJ11259 (Accession NM\_018370). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11259.

FLJ20294 (Accession NM\_017749) is another VGAM816 host target gene. FLJ20294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20294 BINDING SITE, designated SEQ ID:19353, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31609] Another function of VGAM816 is therefore inhibition of FLJ20294 (Accession NM\_017749). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20294. FLJ23604 (Accession NM\_025064) is another VGAM816 host target gene. FLJ23604 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23604, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23604 BINDING SITE, designated SEQ ID:24662, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3527.

[31610] Another function of VGAM816 is therefore inhibition of FLJ23604 (Accession NM\_025064). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23604. Junctional Adhesion Molecule 1 (JAM1, Accession NM\_144501) is another VGAM816 host target gene. JAM1 BINDING SITE1 through JAM1 BINDING SITE5 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by JAM1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JAM1 BINDING SITE1 through JAM1 BINDING SITE5, designated SEQ ID:29323, SEQ ID:29332, SEQ ID:29353, SEQ ID:29343 and SEQ ID:18865 respectively, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31611] Another function of VGAM816 is therefore inhibition of Junctional Adhesion Molecule 1 (JAM1, Accession NM\_144501). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JAM1. KIAA0339 (Accession

XM\_049380) is another VGAM816 host target gene.

KIAA0339 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0339, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0339 BINDING SITE, designated SEQ ID:35405, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31612] Another function of VGAM816 is therefore inhibition of KIAA0339 (Accession XM\_049380). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0339. KIAA0350 (Accession XM\_028332) is another VGAM816 host target gene. KIAA0350 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0350 BINDING SITE, designated SEQ ID:30673, to the nucleotide sequence of VGAM816 RNA, herein designated

VGAM RNA, also designated SEQ ID:3527.

[31613] Another function of VGAM816 is therefore inhibition of KIAA0350 (Accession XM\_028332). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0350. KIAA1795 (Accession XM\_050988) is another VGAM816 host target gene. KIAA1795 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1795, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1795 BINDING SITE, designated SEQ ID:35704, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31614] Another function of VGAM816 is therefore inhibition of KIAA1795 (Accession XM\_050988). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1795. PEF (Accession NM\_012392) is another VGAM816 host target gene. PEF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PEF, corresponding to a HOST TAR-

GET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PEF BINDING SITE, designated SEQ ID:14748, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31615] Another function of VGAM816 is therefore inhibition of PEF (Accession NM\_012392). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PEF. PRIC285 (Accession XM\_028918) is another VGAM816 host target gene. PRIC285 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRIC285, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRIC285 BINDING SITE, designated SEQ ID:30806, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31616] Another function of VGAM816 is therefore inhibition of PRIC285 (Accession XM\_028918). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with PRIC285. Regulator of G-protein Signalling 20 (RGS20, Accession NM\_003702) is another VGAM816 host target gene. RGS20 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RGS20, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RGS20 BINDING SITE, designated SEQ ID:9803, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31617] Another function of VGAM816 is therefore inhibition of Regulator of G-protein Signalling 20 (RGS20, Accession NM\_003702). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RGS20. LOC120114 (Accession XM\_061871) is another VGAM816 host target gene. LOC120114 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC120114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120114 BINDING SITE, desig-

nated SEQ ID:37216, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31618] Another function of VGAM816 is therefore inhibition of LOC120114 (Accession XM\_061871). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120114. LOC144817 (Accession XM\_084972) is another VGAM816 host target gene. LOC144817 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144817, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144817 BINDING SITE, designated SEQ ID:37789, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31619] Another function of VGAM816 is therefore inhibition of LOC144817 (Accession XM\_084972). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144817. LOC151196 (Accession XM\_098019) is another VGAM816 host target gene. LOC151196 BINDING

SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151196 BINDING SITE, designated SEQ ID:41318, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31620] Another function of VGAM816 is therefore inhibition of LOC151196 (Accession XM\_098019). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151196. LOC196955 (Accession XM\_085210) is another VGAM816 host target gene. LOC196955 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196955, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196955 BINDING SITE, designated SEQ ID:37940, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31621] Another function of VGAM816 is therefore inhibition of

LOC196955 (Accession XM\_085210). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196955. LOC200081 (Accession XM\_114110) is another VGAM816 host target gene. LOC200081 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200081, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200081 BINDING SITE, designated SEQ ID:42706, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31622] Another function of VGAM816 is therefore inhibition of LOC200081 (Accession XM\_114110). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200081. LOC200488 (Accession XM\_117240) is another VGAM816 host target gene. LOC200488 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200488, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC200488 BINDING SITE, designated SEQ ID:43316, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31623] Another function of VGAM816 is therefore inhibition of LOC200488 (Accession XM\_117240). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200488. LOC58489 (Accession XM\_051862) is another VGAM816 host target gene. LOC58489 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC58489, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC58489 BINDING SITE, designated SEQ ID:35909, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31624] Another function of VGAM816 is therefore inhibition of LOC58489 (Accession XM\_051862). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC58489. LOC92609 (Accession XM\_053074) is another

VGAM816 host target gene. LOC92609 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92609, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92609 BINDING SITE, designated SEQ ID:36062, to the nucleotide sequence of VGAM816 RNA, herein designated VGAM RNA, also designated SEQ ID:3527.

[31625] Another function of VGAM816 is therefore inhibition of LOC92609 (Accession XM\_053074). Accordingly, utilities of VGAM816 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92609. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 817 (VGAM817) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31626] VGAM817 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM817 was detected is described

hereinabove with reference to Figs. 1–8.

[31627] VGAM817 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus.

VGAM817 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31628] VGAM817 gene encodes a VGAM817 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM817 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM817 precursor RNA is designated SEQ ID:803, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:803 is located at position 19278 relative to the genome of Monkeypox Virus.

[31629] VGAM817 precursor RNA folds onto itself, forming VGAM817 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31630] An enzyme complex designated DICER COMPLEX, `dices` the VGAM817 folded precursor RNA into VGAM817 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM817 RNA is designated SEQ ID:3528, and is provided hereinbelow with reference to the sequence listing part.

[31631] VGAM817 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM817 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM817 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31632] VGAM817 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-



cated in untranslated regions of VGAM817 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM817 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM817 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM817 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31633] The complementary binding of VGAM817 RNA, herein designated VGAM RNA, to host target binding sites on VGAM817 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM817 host target RNA into VGAM817 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31634] It is appreciated that VGAM817 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM817 host target genes. The mRNA of each one of this plurality of VGAM817 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM817 RNA, herein designated VGAM RNA, and which when bound by VGAM817 RNA causes inhibition of translation of respective one or more VGAM817 host target proteins.

[31635] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM817 gene, herein designated VGAM GENE, on one or more VGAM817 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31636] It is yet further appreciated that a function of VGAM817 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM817 correlate with, and may be deduced from, the identity of the host target genes which VGAM817 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31637] Nucleotide sequences of the VGAM817 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM817 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM817 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM817 are further described hereinbelow with reference to Table 1.

[31638] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM817 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM817 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31639] As mentioned hereinabove with reference to Fig. 1, a function of VGAM817 gene, herein designated VGAM is inhibition of expression of VGAM817 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM817 correlate with, and may be deduced from, the identity of the target genes which VGAM817 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31640] Autocrine Motility Factor Receptor (AMFR, Accession NM\_138958) is a VGAM817 host target gene. AMFR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AMFR, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AMFR BINDING SITE, designated SEQ ID:29064, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31641] A function of VGAM817 is therefore inhibition of Autocrine Motility Factor Receptor (AMFR, Accession NM\_138958), a gene which acts to stimulate migration of fibrosarcoma cells. Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AMFR. The function of AMFR and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM440. Chromogranin A (parathyroid secretory protein 1) (CHGA, Accession NM\_001275) is another VGAM817 host target gene. CHGA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CHGA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHGA BINDING SITE, designated SEQ ID:6939, to the nucleotide sequence of

VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31642] Another function of VGAM817 is therefore inhibition of Chromogranin A (parathyroid secretory protein 1) (CHGA, Accession NM\_001275), a gene which regulates dense-core secretory granule biogenesis and hormone sequestration . Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHGA. The function of CHGA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM440.Coagulation Factor III (thromboplastin, tissue factor) (F3, Accession XM\_040465) is another VGAM817 host target gene. F3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by F3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F3 BINDING SITE, designated SEQ ID:33297, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31643] Another function of VGAM817 is therefore inhibition of Coagulation Factor III (thromboplastin, tissue factor) (F3, Accession XM\_040465), a gene which functions in normal hemostasis. Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F3. The function of F3 has been established by previous studies. Factor III, a glycoprotein component of cell membranes, is an essential cofactor for factor VII-dependent activation of blood coagulation and activates the extrinsic pathway of blood coagulation in the presence of factor XII and calcium. It may be the primary physiologic initiator of blood coagulation. This may explain why factor III is the only protein in the coagulation pathway for which a congenital deficiency has not been described. Carson et al. (1985) mapped F3 to 1pter-p21 by study of somatic cell hybrids with a species-specific sensitive chromogenic assay. Spicer et al. (1987) isolated cDNA clones for tissue factor. The amino acid sequence deduced from the nucleotide sequence of the cDNAs indicates that tissue factor is synthesized as a higher molecular weight precursor with a leader sequence of 32 amino acids, while the sequence of the mature protein suggests that there are 3 distinct domains: extracellular

(residues 1–219), hydrophobic (residues 220–242), and cytoplasmic (residues 243–263). Scarpati et al. (1987) screened a human placenta cDNA library in lambda-gt11 for expression of tissue factor antigens. Among 4 million recombinant clones screened, one that was positive expressed a protein that shares epitopes with authentic human brain tissue factor. The 1.1-kb cDNA insert encodes a peptide containing the N-terminal protein sequence of brain tissue factor. By means of this clone used in hybridization to flow-sorted human chromosomes, Scarpati et al. (1987) showed that the tissue factor gene is located on chromosome 1. Scarpati et al. (1987) used a RFLP to map factor 3 to proximal 1p by multipoint linkage analysis with probes known to span that region. Judging by the location arrived at by somatic cell hybridization, the location of F3 may be in the region 1p22–p21. By in situ hybridization, Kao et al. (1988) likewise mapped F3 to 1p22–p21. Mackman et al. (1989) presented the complete sequence of the F3 gene. It is 12.4 kb long and has 6 exons separated by 5 introns. Mackman et al. (1990) concluded that the tissue factor promoter is relatively complex. Tissue factor (TF) is an integral membrane glycoprotein that, when exposed to plasma, is a potent procoagu-



lant. As stated earlier, it is believed to be the physiologic initiator of blood coagulation. Toomey et al. (1997) found that, in contrast to findings of earlier studies which showed that TF-null mouse embryos did not survive beyond midgestation, 14% of TF-deficient embryos from a hybrid background escaped this early mortality and survived to birth. On gross and microscopic inspection, these late gestation, TF-deficient embryos appeared normal. Furthermore, the growth and vascularity of TF +/+, TF +/-, and TF -/- teratomas and teratocarcinomas were indistinguishable. Toomey et al. (1997) concluded that tumor-derived TF is not required for tumor growth and angiogenesis and that the combined data do not support an essential role for TF in embryonic vascular development.

[31644] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31645] Mackman, N.; Fowler, B. J.; Edgington, T. S.; Morrissey, J. H. : Functional analysis of the human tissue factor promoter and induction by serum. Proc. Nat. Acad. Sci. 87: 2254-2258, 1990. ; and

[31646] Toomey, J. R.; Kratzer, K. E.; Lasky, N. M.; Broze, G. J., Jr. : Effect of tissue factor deficiency on mouse and tumor de-

velopment. Proc. Nat. Acad. Sci. 94: 6922–6926, 1997.

[31647] Further studies establishing the function and utilities of F3 are found in John Hopkins OMIM database record ID 134390, and in cited publications numbered 95–9 and 3181–91 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Junctophilin 3 (JPH3, Accession NM\_020655) is another VGAM817 host target gene. JPH3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JPH3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JPH3 BINDING SITE, designated SEQ ID:21825, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31648] Another function of VGAM817 is therefore inhibition of Junctophilin 3 (JPH3, Accession NM\_020655), a gene which is involved in cytoskeletal organization and cellular growth. Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JPH3. The function of JPH3 and its association with various diseases and clinical conditions,

has been established by previous studies, as described hereinabove with reference to VGAM254. Zinc Finger Protein 192 (ZNF192, Accession NM\_006298) is another VGAM817 host target gene. ZNF192 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF192, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF192 BINDING SITE, designated SEQ ID:12988, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31649] Another function of VGAM817 is therefore inhibition of Zinc Finger Protein 192 (ZNF192, Accession NM\_006298). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF192. Chromosome 1 Open Reading Frame 17 (C1orf17, Accession XM\_042965) is another VGAM817 host target gene. C1orf17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1orf17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of C1orf17 BINDING SITE, designated SEQ ID:33852, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31650] Another function of VGAM817 is therefore inhibition of Chromosome 1 Open Reading Frame 17 (C1orf17, Accession XM\_042965). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf17. Elongation of Very Long Chain Fatty Acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 1 (ELOVL1, Accession NM\_022821) is another VGAM817 host target gene. ELOVL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ELOVL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELOVL1 BINDING SITE, designated SEQ ID:23099, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31651] Another function of VGAM817 is therefore inhibition of Elongation of Very Long Chain Fatty Acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 1 (ELOVL1, Accession NM\_022821).

Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELOVL1. FLJ10842 (Accession NM\_018238) is another VGAM817 host target gene. FLJ10842 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10842, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10842 BINDING SITE, designated SEQ ID:20187, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31652] Another function of VGAM817 is therefore inhibition of FLJ10842 (Accession NM\_018238). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10842. FLJ22969 (Accession XM\_044006) is another VGAM817 host target gene. FLJ22969 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22969, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ22969 BINDING SITE, designated SEQ ID:34067, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31653] Another function of VGAM817 is therefore inhibition of FLJ22969 (Accession XM\_044006). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22969. FLJ23519 (Accession NM\_032240) is another VGAM817 host target gene. FLJ23519 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23519 BINDING SITE, designated SEQ ID:25971, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31654] Another function of VGAM817 is therefore inhibition of FLJ23519 (Accession NM\_032240). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23519. KIAA0876 (Accession XM\_035625) is another VGAM817

host target gene. KIAA0876 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0876, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0876 BINDING SITE, designated SEQ ID:32294, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31655] Another function of VGAM817 is therefore inhibition of KIAA0876 (Accession XM\_035625). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0876. KIAA0961 (Accession NM\_014898) is another VGAM817 host target gene. KIAA0961 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0961, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0961 BINDING SITE, designated SEQ ID:17071, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31656] Another function of VGAM817 is therefore inhibition of KIAA0961 (Accession NM\_014898). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0961. KIAA1265 (Accession XM\_047707) is another VGAM817 host target gene. KIAA1265 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1265, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1265 BINDING SITE, designated SEQ ID:35034, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31657] Another function of VGAM817 is therefore inhibition of KIAA1265 (Accession XM\_047707). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1265. KIAA1678 (Accession XM\_051221) is another VGAM817 host target gene. KIAA1678 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1678, corresponding to a HOST TARGET binding site such as BINDING SITE I,



BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1678 BINDING SITE, designated SEQ ID:35788, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31658] Another function of VGAM817 is therefore inhibition of KIAA1678 (Accession XM\_051221). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1678. RAB17, Member RAS Oncogene Family (RAB17, Accession NM\_022449) is another VGAM817 host target gene. RAB17 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by RAB17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB17 BINDING SITE, designated SEQ ID:22787, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31659] Another function of VGAM817 is therefore inhibition of RAB17, Member RAS Oncogene Family (RAB17, Accession NM\_022449). Accordingly, utilities of VGAM817 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB17. Solute Carrier Family 6 (neurotransmitter transporter), Member 14 (SLC6A14, Accession NM\_007231) is another VGAM817 host target gene. SLC6A14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC6A14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC6A14 BINDING SITE, designated SEQ ID:14100, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31660] Another function of VGAM817 is therefore inhibition of Solute Carrier Family 6 (neurotransmitter transporter), Member 14 (SLC6A14, Accession NM\_007231). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC6A14. LOC146229 (Accession XM\_085387) is another VGAM817 host target gene. LOC146229 BINDING SITE1 and LOC146229 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC146229, corresponding to HOST TARGET

binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146229 BINDING SITE1 and LOC146229 BINDING SITE2, designated SEQ ID:38104 and SEQ ID:38105 respectively, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31661] Another function of VGAM817 is therefore inhibition of LOC146229 (Accession XM\_085387). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146229. LOC164395 (Accession XM\_092778) is another VGAM817 host target gene. LOC164395 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC164395, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164395 BINDING SITE, designated SEQ ID:40145, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31662] Another function of VGAM817 is therefore inhibition of LOC164395 (Accession XM\_092778). Accordingly, utilities

of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC164395. LOC196337 (Accession XM\_113696) is another VGAM817 host target gene. LOC196337 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196337 BINDING SITE, designated SEQ ID:42358, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31663] Another function of VGAM817 is therefore inhibition of LOC196337 (Accession XM\_113696). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196337. LOC200197 (Accession XM\_114148) is another VGAM817 host target gene. LOC200197 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200197, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC200197 BINDING SITE, designated SEQ ID:42730, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31664] Another function of VGAM817 is therefore inhibition of LOC200197 (Accession XM\_114148). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200197. LOC200681 (Accession XM\_117260) is another VGAM817 host target gene. LOC200681 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200681, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200681 BINDING SITE, designated SEQ ID:43341, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31665] Another function of VGAM817 is therefore inhibition of LOC200681 (Accession XM\_117260). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200681. LOC51301 (Accession NM\_016591) is another VGAM817 host target gene. LOC51301 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51301, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51301 BINDING SITE, designated SEQ ID:18670, to the nucleotide sequence of VGAM817 RNA, herein designated VGAM RNA, also designated SEQ ID:3528.

[31666] Another function of VGAM817 is therefore inhibition of LOC51301 (Accession NM\_016591). Accordingly, utilities of VGAM817 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51301. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 818 (VGAM818) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31667] VGAM818 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM818 was detected is described hereinabove with reference to Figs. 1-8.

[31668] VGAM818 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus.

VGAM818 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31669] VGAM818 gene encodes a VGAM818 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM818 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM818 precursor RNA is designated SEQ ID:804, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:804 is located at position 27338 relative to the genome of Monkeypox Virus.

[31670] VGAM818 precursor RNA folds onto itself, forming VGAM818 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[31671] An enzyme complex designated DICER COMPLEX, `dices` the VGAM818 folded precursor RNA into VGAM818 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM818 RNA is designated SEQ ID:3529, and is provided hereinbelow with reference to the sequence listing part.

[31672] VGAM818 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM818 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM818 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31673] VGAM818 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM818 host target



RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM818 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM818 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM818 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31674] The complementary binding of VGAM818 RNA, herein designated VGAM RNA, to host target binding sites on VGAM818 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM818 host target RNA into VGAM818 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31675] It is appreciated that VGAM818 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM818 host target genes. The mRNA of each one of this plurality of VGAM818 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM818 RNA, herein designated VGAM RNA, and which when bound by VGAM818 RNA causes inhibition of translation of respective one or more VGAM818 host target proteins.

[31676] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM818 gene, herein designated VGAM GENE, on one or more VGAM818 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31677] It is yet further appreciated that a function of VGAM818 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM818 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM818 correlate with, and may be deduced from, the identity of the host target genes which VGAM818 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31678] Nucleotide sequences of the VGAM818 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM818 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM818 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM818 are further described hereinbelow with reference to Table 1.

[31679] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM818 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM818 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31680] As mentioned hereinabove with reference to Fig. 1, a function of VGAM818 gene, herein designated VGAM is inhibition of expression of VGAM818 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM818 correlate with, and may be deduced from, the identity of the target genes which VGAM818 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31681] Apical Protein-like (*Xenopus laevis*) (APXL, Accession NM\_001649) is a VGAM818 host target gene. APXL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APXL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates

the complementarity of the nucleotide sequences of APXL BINDING SITE, designated SEQ ID:7353, to the nucleotide sequence of VGAM818 RNA, herein designated VGAM RNA, also designated SEQ ID:3529.

[31682] A function of VGAM818 is therefore inhibition of Apical Protein-like (*Xenopus laevis*) (APXL, Accession NM\_001649), a gene which is implicated in amiloride-sensitive sodium channel activity. Accordingly, utilities of VGAM818 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APXL. The function of APXL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152.LOC150142 (Accession XM\_086791) is another VGAM818 host target gene. LOC150142 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150142 BINDING SITE, designated SEQ ID:38849, to the nucleotide sequence of VGAM818 RNA, herein designated VGAM RNA, also designated SEQ ID:3529.

[31683] Another function of VGAM818 is therefore inhibition of LOC150142 (Accession XM\_086791). Accordingly, utilities of VGAM818 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150142. LOC202316 (Accession XM\_117380) is another VGAM818 host target gene. LOC202316 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202316 BINDING SITE, designated SEQ ID:43424, to the nucleotide sequence of VGAM818 RNA, herein designated VGAM RNA, also designated SEQ ID:3529.

[31684] Another function of VGAM818 is therefore inhibition of LOC202316 (Accession XM\_117380). Accordingly, utilities of VGAM818 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202316. LOC90190 (Accession XM\_029758) is another VGAM818 host target gene. LOC90190 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90190, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90190 BINDING SITE, designated SEQ ID:30945, to the nucleotide sequence of VGAM818 RNA, herein designated VGAM RNA, also designated SEQ ID:3529.

[31685] Another function of VGAM818 is therefore inhibition of LOC90190 (Accession XM\_029758). Accordingly, utilities of VGAM818 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90190. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 819 (VGAM819) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31686] VGAM819 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM819 was detected is described hereinabove with reference to Figs. 1–8.

[31687] VGAM819 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ateline Herpesvirus 3. VGAM819 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[31688] VGAM819 gene encodes a VGAM819 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM819 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM819 precursor RNA is designated SEQ ID:805, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:805 is located at position 92255 relative to the genome of Ate-line Herpesvirus 3.

[31689] VGAM819 precursor RNA folds onto itself, forming VGAM819 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31690] An enzyme complex designated DICER COMPLEX, `dices` the VGAM819 folded precursor RNA into VGAM819 RNA,



herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM819 RNA is designated SEQ ID:3530, and is provided hereinbelow with reference to the sequence listing part.

[31691] VGAM819 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM819 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM819 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31692] VGAM819 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM819 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM819 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM819 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM819 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31693] The complementary binding of VGAM819 RNA, herein designated VGAM RNA, to host target binding sites on VGAM819 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM819 host target RNA into VGAM819 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[31694] It is appreciated that VGAM819 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM819 host target genes. The mRNA of each one of this plurality of VGAM819 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM819 RNA, herein designated VGAM RNA, and which when bound by VGAM819 RNA causes inhibition of translation of respective one or more VGAM819 host target proteins.

[31695] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM819 gene, herein designated VGAM GENE, on one or more VGAM819 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31696] It is yet further appreciated that a function of VGAM819 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM819 include diagnosis, prevention and treatment of viral infection by Ateline Herpesvirus 3. Specific functions, and accordingly utilities, of VGAM819 correlate with, and may be deduced from, the identity of the host target genes which VGAM819 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31697] Nucleotide sequences of the VGAM819 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM819 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM819 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM819 are further described hereinbelow with reference to Table 1.

[31698] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM819 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM819 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31699] As mentioned hereinabove with reference to Fig. 1, a function of VGAM819 gene, herein designated VGAM is inhibition of expression of VGAM819 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM819 correlate with, and may be deduced from, the identity of the target genes which VGAM819 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31700] Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_000109) is a VGAM819 host target gene. DMD BINDING SITE1 through DMD BINDING SITE13 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DMD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DMD BINDING SITE1 through DMD BINDING SITE13, designated SEQ

ID:5575, SEQ ID:10158, SEQ ID:10165, SEQ ID:10189, SEQ ID:10206, SEQ ID:10179, SEQ ID:10216, SEQ ID:10240, SEQ ID:10228, SEQ ID:10171, SEQ ID:10184, SEQ ID:10211 and SEQ ID:10201 respectively, to the nucleotide sequence of VGAM819 RNA, herein designated VGAM RNA, also designated SEQ ID:3530.

[31701] A function of VGAM819 is therefore inhibition of Dystrophin (muscular dystrophy, Duchenne and Becker types) (DMD, Accession NM\_000109), a gene which muscular dystrophy . Accordingly, utilities of VGAM819 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DMD. The function of DMD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM218.SSH2 (Accession XM\_030846) is another VGAM819 host target gene. SSH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SSH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSH2 BINDING SITE, designated SEQ ID:31189, to the nucleotide sequence of VGAM819 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3530.

[31702] Another function of VGAM819 is therefore inhibition of SSH2 (Accession XM\_030846). Accordingly, utilities of VGAM819 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSH2. LOC123036 (Accession XM\_058676) is another VGAM819 host target gene. LOC123036 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC123036, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC123036 BINDING SITE, designated SEQ ID:36719, to the nucleotide sequence of VGAM819 RNA, herein designated VGAM RNA, also designated SEQ ID:3530.

[31703] Another function of VGAM819 is therefore inhibition of LOC123036 (Accession XM\_058676). Accordingly, utilities of VGAM819 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC123036. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 820 (VGAM820) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31704] VGAM820 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM820 was detected is described hereinabove with reference to Figs. 1–8.

[31705] VGAM820 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saimiriine Herpesvirus 2. VGAM820 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31706] VGAM820 gene encodes a VGAM820 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM820 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM820 precursor RNA is designated SEQ ID:806, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:806 is located at position 97653 relative to the genome of Saimiriine Herpesvirus 2.

[31707] VGAM820 precursor RNA folds onto itself, forming



VGAM820 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31708] An enzyme complex designated DICER COMPLEX, `dices` the VGAM820 folded precursor RNA into VGAM820 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM820 RNA is designated SEQ ID:3531, and is provided hereinbelow with reference to the sequence listing part.

[31709] VGAM820 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM820 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM820 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31710] VGAM820 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM820 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM820 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM820 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM820 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31711] The complementary binding of VGAM820 RNA, herein designated VGAM RNA, to host target binding sites on VGAM820 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM820 host target RNA into VGAM820 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31712] It is appreciated that VGAM820 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM820 host target genes. The mRNA of each one of this plurality of VGAM820 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM820 RNA, herein designated VGAM RNA, and which when bound by VGAM820 RNA causes inhibition of translation of respective one or more VGAM820 host target proteins.

[31713] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM820 gene, herein designated VGAM GENE, on one or more VGAM820 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31714] It is yet further appreciated that a function of VGAM820 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM820 include diagnosis, prevention and treatment of viral infection by Saimiriine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM820 correlate with, and may be deduced from, the identity of the host target genes which VGAM820 binds and inhibits,

and the function of these host target genes, as elaborated hereinbelow.

[31715] Nucleotide sequences of the VGAM820 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM820 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM820 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM820 are further described hereinbelow with reference to Table 1.

[31716] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM820 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM820 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31717] As mentioned hereinabove with reference to Fig. 1, a function of VGAM820 gene, herein designated VGAM is inhibition of expression of VGAM820 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM820 correlate with, and may be deduced from, the identity of the target genes which VGAM820 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[31718] Kelch-like 3 (Drosophila) (KLHL3, Accession XM\_113450) is a VGAM820 host target gene. KLHL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KLHL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KLHL3 BINDING SITE, designated SEQ ID:42265, to the nucleotide sequence of VGAM820 RNA, herein designated VGAM RNA, also designated SEQ ID:3531.

[31719] A function of VGAM820 is therefore inhibition of Kelch-like 3 (Drosophila) (KLHL3, Accession XM\_113450). Accordingly, utilities of VGAM820 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KLHL3. Protocadherin 11 X-linked (PCDH11X, Accession NM\_032969) is another VGAM820 host target gene. PCDH11X BINDING SITE1 and PCDH11X BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PCDH11X, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of PCDH11X BINDING SITE1 and PCDH11X BINDING SITE2, designated SEQ ID:26801 and SEQ ID:26786 respectively, to the nucleotide sequence of VGAM820 RNA, herein designated VGAM RNA, also designated SEQ ID:3531.

[31720] Another function of VGAM820 is therefore inhibition of Protocadherin 11 X-linked (PCDH11X, Accession NM\_032969), a gene which is thought to play a fundamental role in cell-cell recognition essential for the segmental development and function of the central nervous system. Accordingly, utilities of VGAM820 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH11X. The function of PCDH11X and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM433.FLJ12476 (Accession NM\_022784) is another VGAM820 host target gene. FLJ12476 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12476, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12476 BINDING SITE, designated SEQ ID:23067, to the nucleotide

sequence of VGAM820 RNA, herein designated VGAM RNA, also designated SEQ ID:3531.

- [31721] Another function of VGAM820 is therefore inhibition of FLJ12476 (Accession NM\_022784). Accordingly, utilities of VGAM820 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12476. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 821 (VGAM821) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [31722] VGAM821 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM821 was detected is described hereinabove with reference to Figs. 1–8.
- [31723] VGAM821 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 6. VGAM821 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.
- [31724] VGAM821 gene encodes a VGAM821 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other



miRNA genes, and unlike most ordinary genes, VGAM821 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM821 precursor RNA is designated SEQ ID:807, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:807 is located at position 120037 relative to the genome of Human Herpesvirus 6.

[31725] VGAM821 precursor RNA folds onto itself, forming VGAM821 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31726] An enzyme complex designated DICER COMPLEX, `dices` the VGAM821 folded precursor RNA into VGAM821 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 90%) nucleotide sequence of VGAM821 RNA is designated SEQ ID:3532, and is provided hereinbelow with reference to the sequence listing part.

[31727] VGAM821 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM821 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM821 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31728] VGAM821 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM821 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM821 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM821 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM821 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31729] The complementary binding of VGAM821 RNA, herein designated VGAM RNA, to host target binding sites on VGAM821 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM821 host target RNA into VGAM821 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31730] It is appreciated that VGAM821 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM821 host target genes. The mRNA of

each one of this plurality of VGAM821 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM821 RNA, herein designated VGAM RNA, and which when bound by VGAM821 RNA causes inhibition of translation of respective one or more VGAM821 host target proteins.

[31731] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM821 gene, herein designated VGAM GENE, on one or more VGAM821 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[31732] It is yet further appreciated that a function of VGAM821 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 6. Specific functions, and accordingly utilities, of VGAM821 correlate with, and may be deduced from, the identity of the host target genes which VGAM821 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31733] Nucleotide sequences of the VGAM821 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM821 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM821 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM821 are further described hereinbelow with reference to Table 1.

[31734] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM821 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM821 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[31735] As mentioned hereinabove with reference to Fig. 1, a function of VGAM821 gene, herein designated VGAM is inhibition of expression of VGAM821 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM821 correlate with, and may be deduced from, the identity of the target genes which VGAM821 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31736] Deoxyguanosine Kinase (DGUOK, Accession NM\_080915) is a VGAM821 host target gene. DGUOK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DGUOK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DGUOK BINDING SITE, designated SEQ ID:28133, to the nucleotide sequence of VGAM821 RNA, herein designated VGAM RNA, also designated SEQ ID:3532.

[31737] A function of VGAM821 is therefore inhibition of Deoxyguanosine Kinase (DGUOK, Accession NM\_080915), a gene which is deoxyguanosine kinase and mediates phos-

phorylation of several deoxyribonucleosides. Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DGUOK. The function of DGUOK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM121. Deleted In Lung and Esophageal Cancer 1 (DLEC1, Accession NM\_007336) is another VGAM821 host target gene. DLEC1 BINDING SITE1 and DLEC1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by DLEC1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLEC1 BINDING SITE1 and DLEC1 BINDING SITE2, designated SEQ ID:14263 and SEQ ID:14269 respectively, to the nucleotide sequence of VGAM821 RNA, herein designated VGAM RNA, also designated SEQ ID:3532.

[31738] Another function of VGAM821 is therefore inhibition of Deleted In Lung and Esophageal Cancer 1 (DLEC1, Accession NM\_007336). Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with DLEC1. Neuronal Pentraxin I (NPTX1, Accession NM\_002522) is another VGAM821 host target gene. NPTX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NPTX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NPTX1 BINDING SITE, designated SEQ ID:8352, to the nucleotide sequence of VGAM821 RNA, herein designated VGAM RNA, also designated SEQ ID:3532.

[31739] Another function of VGAM821 is therefore inhibition of Neuronal Pentraxin I (NPTX1, Accession NM\_002522), a gene which may be involved in synaptic uptake of extracellular material and is very strongly similar to rat NP1. Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NPTX1. The function of NPTX1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM111. Suppressor of Fused Homolog (Drosophila) (SUFU, Accession NM\_016169) is another VGAM821 host target gene. SUFU BINDING SITE is



HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SUFU, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SUFU BINDING SITE, designated SEQ ID:18249, to the nucleotide sequence of VGAM821 RNA, herein designated VGAM RNA, also designated SEQ ID:3532.

[31740] Another function of VGAM821 is therefore inhibition of Suppressor of Fused Homolog (Drosophila) (SUFU, Accession NM\_016169). Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SUFU. CG012 (Accession XM\_096710) is another VGAM821 host target gene. CG012 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CG012, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CG012 BINDING SITE, designated SEQ ID:40491, to the nucleotide sequence of VGAM821 RNA, herein designated VGAM RNA, also designated SEQ ID:3532.

[31741] Another function of VGAM821 is therefore inhibition of CG012 (Accession XM\_096710). Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CG012. FLJ20396 (Accession NM\_017801) is another VGAM821 host target gene. FLJ20396 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20396, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20396 BINDING SITE, designated SEQ ID:19445, to the nucleotide sequence of VGAM821 RNA, herein designated VGAM RNA, also designated SEQ ID:3532.

[31742] Another function of VGAM821 is therefore inhibition of FLJ20396 (Accession NM\_017801). Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20396. KIAA0276 (Accession XM\_048199) is another VGAM821 host target gene. KIAA0276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0276 BINDING SITE, designated SEQ ID:35134, to the nucleotide sequence of VGAM821 RNA, herein designated VGAM RNA, also designated SEQ ID:3532.

[31743] Another function of VGAM821 is therefore inhibition of KIAA0276 (Accession XM\_048199). Accordingly, utilities of VGAM821 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0276. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 822 (VGAM822) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31744] VGAM822 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM822 was detected is described hereinabove with reference to Figs. 1–8.

[31745] VGAM822 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 6. VGAM822 host target gene, herein designated VGAM

HOST TARGET GENE, is a human gene contained in the human genome.

[31746] VGAM822 gene encodes a VGAM822 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM822 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM822 precursor RNA is designated SEQ ID:808, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:808 is located at position 117925 relative to the genome of Human Herpesvirus 6.

[31747] VGAM822 precursor RNA folds onto itself, forming VGAM822 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31748] An enzyme complex designated DICER COMPLEX, `dices` the VGAM822 folded precursor RNA into VGAM822 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM822 RNA is designated SEQ ID:3533, and is provided hereinbelow with reference to the sequence listing part.

[31749] VGAM822 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM822 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM822 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31750] VGAM822 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM822 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM822 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM822 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM822 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31751] The complementary binding of VGAM822 RNA, herein designated VGAM RNA, to host target binding sites on VGAM822 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM822 host target RNA into VGAM822 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[31752] It is appreciated that VGAM822 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM822 host target genes. The mRNA of each one of this plurality of VGAM822 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM822 RNA, herein designated VGAM RNA, and which when bound by VGAM822 RNA causes inhibition of translation of respective one or more VGAM822 host target proteins.

[31753] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM822 gene, herein designated VGAM GENE, on one or more VGAM822 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31754] It is yet further appreciated that a function of VGAM822 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM822 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 6. Specific functions, and accordingly utilities, of VGAM822 correlate with, and may be deduced from, the identity of the host target genes which VGAM822 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31755] Nucleotide sequences of the VGAM822 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM822 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM822 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM822 are further described hereinbelow with reference to Table 1.

[31756] Nucleotide sequences of host target binding sites, such as



BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM822 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM822 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31757] As mentioned hereinabove with reference to Fig. 1, a function of VGAM822 gene, herein designated VGAM is inhibition of expression of VGAM822 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM822 correlate with, and may be deduced from, the identity of the target genes which VGAM822 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31758] V-maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog (avian) (MAF, Accession NM\_005360) is a VGAM822 host target gene. MAF BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MAF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAF BINDING SITE, designated SEQ ID:11838, to the nucleotide sequence of VGAM822

RNA, herein designated VGAM RNA, also designated SEQ ID:3533.

[31759] A function of VGAM822 is therefore inhibition of V-maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog (avian) (MAF, Accession NM\_005360), a gene which is a transcription factor; contains a leucine zipper motif. Accordingly, utilities of VGAM822 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAF. The function of MAF has been established by previous studies. Nishizawa et al. (1989) identified in the human genome a cellular analog of v-maf which was isolated from the provirus of the avian musculoaponeurotic fibrosarcoma virus AS42. The deduced amino acid sequence of the v-maf gene product contains a leucine zipper motif similar to that found in a number of DNA binding proteins, including the gene products of the FOS (OMIM Ref. No. 164810), JUN (OMIM Ref. No. 165160), and MYC (OMIM Ref. No. 190080) oncogenes. Through the use of a cDNA probe for in situ hybridization, Yoshida et al. (1991) localized the MAF gene to 16q22-q23. Blank and Andrews (1997) reviewed the MAF transcription factors, a unique subclass of basic-leucine zipper transcription (bZIP) factors. Members of the MAF

family appear to play important roles in the regulation of differentiation. Human congenital cataract and ocular anterior segment dysgenesis both demonstrate extensive genetic and phenotypic heterogeneity. Kim et al. (1999) demonstrated that the homozygous null mutant Maf mouse embryo exhibits defective lens formation and microphthalmia. Jamieson et al. (2002) identified a family where ocular developmental abnormalities (cataract, anterior segment dysgenesis, and microphthalmia) cosegregated with a translocation, t(5;16)(p15.3;q23.2), in both balanced and unbalanced forms. Cloning the 16q23.2 breakpoint demonstrated that it transected the genomic-control domain of MAF. The 16q23.2 breakpoint transected the common fragile site FRA16D (see OMIM Ref. No. 605131), providing a molecular demonstration of a germline break in a common fragile site. Through mutation screening of a panel of patients with hereditary congenital cataract, Jamieson et al. (2002) identified a mutation in the MAF gene in a 3-generation family with cataract, microcornea, and iris coloboma

[31760] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [31761] Jamieson, R. V.; Perveen, R.; Kerr, B.; Carette, M.; Yardley, J.; Heon, E.; Wirth, M. G.; van Heyningen, V.; Donnai, D.; Munier, F.; Black, G. C. M. : Domain disruption and mutation of the bZIP transcription factor, MAF, associated with cataract, ocular anterior segment dysgenesis and coloboma. *Hum. Molec. Genet.* 11: 33–42, 2002. ; and
- [31762] Kim, J. I.; Li, T.; Ho, I. C.; Grusby, M. J.; Glimcher, L. H. : Requirement for the c-Maf transcription factor in crystallin gene regulation and lens development. *Proc. Nat. Acad. Sci.* 96:.
- [31763] Further studies establishing the function and utilities of MAF are found in John Hopkins OMIM database record ID 177075, and in cited publications numbered 10095–10099 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445) is another VGAM822 host target gene. GRIN3A BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by GRIN3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

GRIN3A BINDING SITE, designated SEQ ID:28532, to the nucleotide sequence of VGAM822 RNA, herein designated VGAM RNA, also designated SEQ ID:3533.

[31764] Another function of VGAM822 is therefore inhibition of Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445). Accordingly, utilities of VGAM822 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRIN3A. KIAA1879 (Accession XM\_056635) is another VGAM822 host target gene. KIAA1879 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1879, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1879 BINDING SITE, designated SEQ ID:36408, to the nucleotide sequence of VGAM822 RNA, herein designated VGAM RNA, also designated SEQ ID:3533.

[31765] Another function of VGAM822 is therefore inhibition of KIAA1879 (Accession XM\_056635). Accordingly, utilities of VGAM822 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1879. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 823 (VGAM823) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31766] VGAM823 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM823 was detected is described hereinabove with reference to Figs. 1–8.

[31767] VGAM823 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM823 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31768] VGAM823 gene encodes a VGAM823 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM823 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM823 precursor RNA is designated SEQ ID:809, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:809 is

located at position 2329 relative to the genome of African Swine Fever Virus.

[31769] VGAM823 precursor RNA folds onto itself, forming VGAM823 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31770] An enzyme complex designated DICER COMPLEX, `dices` the VGAM823 folded precursor RNA into VGAM823 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 61%) nucleotide sequence of VGAM823 RNA is designated SEQ ID:3534, and is provided hereinbelow with reference to the sequence listing part.

[31771] VGAM823 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM823 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM823 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[31772] VGAM823 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM823 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM823 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM823 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM823 host target RNA,



herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31773] The complementary binding of VGAM823 RNA, herein designated VGAM RNA, to host target binding sites on VGAM823 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM823 host target RNA into VGAM823 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31774] It is appreciated that VGAM823 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM823 host target genes. The mRNA of each one of this plurality of VGAM823 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM823 RNA, herein designated VGAM RNA, and which when bound by VGAM823 RNA causes inhibition of translation of respective one or more VGAM823

host target proteins.

[31775] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM823 gene, herein designated VGAM GENE, on one or more VGAM823 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31776] It is yet further appreciated that a function of VGAM823 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM823 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus.

Specific functions, and accordingly utilities, of VGAM823 correlate with, and may be deduced from, the identity of the host target genes which VGAM823 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [31777] Nucleotide sequences of the VGAM823 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM823 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM823 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM823 are further described hereinbelow with reference to Table 1.
- [31778] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM823 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM823 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [31779] As mentioned hereinabove with reference to Fig. 1, a function of VGAM823 gene, herein designated VGAM is inhibition of expression of VGAM823 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM823 correlate with, and may be deduced from, the identity of the target genes which VGAM823 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31780] Nuclear Factor I/A (NFIA, Accession XM\_046827) is a VGAM823 host target gene. NFIA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NFIA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFIA BINDING SITE, designated SEQ ID:34839, to the nucleotide sequence of VGAM823 RNA, herein designated VGAM RNA, also designated SEQ ID:3534.

[31781] A function of VGAM823 is therefore inhibition of Nuclear Factor I/A (NFIA, Accession XM\_046827). Accordingly, utilities of VGAM823 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NFIA. DKFZP434A043 (Accession NM\_015396) is another VGAM823 host target gene. DKFZP434A043 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434A043, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434A043 BINDING SITE, designated SEQ ID:17700, to the nucleotide sequence of VGAM823 RNA, herein designated VGAM RNA, also designated SEQ ID:3534.

[31782] Another function of VGAM823 is therefore inhibition of DKFZP434A043 (Accession NM\_015396). Accordingly, utilities of VGAM823 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434A043. LOC201799 (Accession XM\_114380) is another VGAM823 host target gene. LOC201799 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC201799, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201799 BINDING SITE, designated SEQ ID:42912, to the nucleotide sequence of VGAM823 RNA, herein designated VGAM RNA, also designated SEQ ID:3534.

[31783] Another function of VGAM823 is therefore inhibition of LOC201799 (Accession XM\_114380). Accordingly, utilities of VGAM823 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC201799. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 824 (VGAM824) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31784] VGAM824 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM824 was detected is described hereinabove with reference to Figs. 1–8.

[31785] VGAM824 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM824 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31786] VGAM824 gene encodes a VGAM824 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM824 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM824 precursor RNA is designated SEQ

ID:810, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:810 is located at position 3473 relative to the genome of African Swine Fever Virus.

[31787] VGAM824 precursor RNA folds onto itself, forming VGAM824 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31788] An enzyme complex designated DICER COMPLEX, `dices` the VGAM824 folded precursor RNA into VGAM824 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM824 RNA is designated SEQ ID:3535, and is provided hereinbelow with reference to the sequence

listing part.

[31789] VGAM824 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM824 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM824 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31790] VGAM824 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM824 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM824 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM824 RNA, herein designated VGAM RNA, may



have a different number of host target binding sites in untranslated regions of a VGAM824 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31791] The complementary binding of VGAM824 RNA, herein designated VGAM RNA, to host target binding sites on VGAM824 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM824 host target RNA into VGAM824 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31792] It is appreciated that VGAM824 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM824 host target genes. The mRNA of each one of this plurality of VGAM824 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM824 RNA, herein designated VGAM

RNA, and which when bound by VGAM824 RNA causes inhibition of translation of respective one or more VGAM824 host target proteins.

[31793] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM824 gene, herein designated VGAM GENE, on one or more VGAM824 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31794] It is yet further appreciated that a function of VGAM824 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM824 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus. Specific functions, and accordingly utilities, of VGAM824 correlate with, and may be deduced from, the identity of the host target genes which VGAM824 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31795] Nucleotide sequences of the VGAM824 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM824 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM824 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM824 are further described hereinbelow with reference to Table 1.

[31796] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM824 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM824 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31797] As mentioned hereinabove with reference to Fig. 1, a function of VGAM824 gene, herein designated VGAM is

inhibition of expression of VGAM824 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM824 correlate with, and may be deduced from, the identity of the target genes which VGAM824 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31798] Coagulation Factor C Homolog, Cochlin (*Limulus polyphemus*) (COCH, Accession NM\_004086) is a VGAM824 host target gene. COCH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by COCH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of COCH BINDING SITE, designated SEQ ID:10290, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31799] A function of VGAM824 is therefore inhibition of Coagulation Factor C Homolog, Cochlin (*Limulus polyphemus*) (COCH, Accession NM\_004086). Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COCH. Fyn-related Kinase (FRK, Accession NM\_002031) is an-

other VGAM824 host target gene. FRK BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FRK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FRK BINDING SITE, designated SEQ ID:7786, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31800] Another function of VGAM824 is therefore inhibition of Fyn-related Kinase (FRK, Accession NM\_002031), a gene which binds pRb (RB1) during G1 and S phase and suppresses growth. Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FRK. The function of FRK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM157. Sequestosome 1 (SQSTM1, Accession NM\_003900) is another VGAM824 host target gene. SQSTM1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SQSTM1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SQSTM1 BINDING SITE, designated SEQ ID:9987, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31801] Another function of VGAM824 is therefore inhibition of Sequestosome 1 (SQSTM1, Accession NM\_003900), a gene which binds SH2 domain of p56lck and ubiquitin, and it is associated with a serine/threonine kinase activity. Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SQSTM1. The function of SQSTM1 has been established by previous studies. Using 24 French Canadian families and 112 unrelated individuals with Paget disease of bone (OMIM Ref. No. 602080), Laurin et al. (2002) confined the PDB3 locus (OMIM Ref. No. 606262) on 5q35-qter to a region of approximately 300 kb. Within this interval, 2 disease-related haplotype signatures were observed in 11 families and 18 unrelated patients. This region encoded the SQSTM1 gene, which is a candidate gene for PDB because of its association with the RANK pathway (see OMIM Ref. No. 603499). Screening SQSTM1

for mutations led to the identification of a recurrent non-conservative change (P392L; 601530.0001) flanking the ubiquitin-associated domain (UBA; position 394–440) of the protein that was not present in 291 control individuals. The data demonstrated that 2 independent mutational events at the same position in SQSTM1 cause Paget disease of bone in a high proportion of French Canadian patients. The Src homology type 2 (SH2) domain is a highly conserved motif of about 100 amino acids which mediates protein–protein interactions by binding to phosphotyrosine. p56–lck (OMIM Ref. No. 153390), a T–cell–specific src family tyrosine kinase with an SH2 domain, is involved in T–cell signal transduction. A 62–kD protein (p62) was identified by Park et al. (1995) as a ligand of the p56–lck SH2 domain. Park et al. (1995) found that the p56–lck SH2 domain binds to p62 at the ser59 of p62 only when that serine is phosphorylated. Moreover, Park et al. (1995) found that p62 is associated with a serine/threonine kinase activity and also binds to ras GTP–ase–activating protein, a negative regulator of the ras signaling pathway.

[31802] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [31803] Laurin, N.; Brown, J. P.; Morissette, J.; Raymond, V. : Re-current mutation of the gene encoding sequestosome 1 (SQSTM1/p62) in Paget disease of bone. *Am. J. Hum. Genet.* 70: 1582–1588, 2002. ; and
- [31804] Park, I.; Chung, J.; Walsh, C. T.; Yun, Y.; Strominger, J. L.; Shin, J. : Phosphotyrosine-independent binding of a 62-kDa protein to the src homology 2 (SH2) domain of p56-lck and its regu.
- [31805] Further studies establishing the function and utilities of SQSTM1 are found in John Hopkins OMIM database record ID 601530, and in cited publications numbered 154 and 7189–7192 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Titin (TTN, Accession NM\_133378) is another VGAM824 host target gene. TTN BINDING SITE1 through TTN BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TTN, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TTN BINDING SITE1 through TTN BINDING SITE3, designated SEQ ID:28501, SEQ ID:28506 and SEQ ID:28516 respectively, to the nucleotide sequence of VGAM824 RNA, herein des-



ignated VGAM RNA, also designated SEQ ID:3535.

[31806] Another function of VGAM824 is therefore inhibition of Titin (TTN, Accession NM\_133378). Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TTN. DKFZP434O047 (Accession NM\_015594) is another VGAM824 host target gene. DKFZP434O047 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZP434O047, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434O047 BINDING SITE, designated SEQ ID:17861, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31807] Another function of VGAM824 is therefore inhibition of DKFZP434O047 (Accession NM\_015594). Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434O047. Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665) is another VGAM824 host target gene. EVI5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by EVI5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EVI5 BINDING SITE, designated SEQ ID:12212, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31808] Another function of VGAM824 is therefore inhibition of Ecotropic Viral Integration Site 5 (EVI5, Accession NM\_005665). Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EVI5. FENS-1 (Accession NM\_020830) is another VGAM824 host target gene. FENS-1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FENS-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FENS-1 BINDING SITE, designated SEQ ID:21895, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31809] Another function of VGAM824 is therefore inhibition of FENS-1 (Accession NM\_020830). Accordingly, utilities of

VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FENS-1. KIAA1432 (Accession XM\_039698) is another VGAM824 host target gene. KIAA1432 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1432, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1432 BINDING SITE, designated SEQ ID:33146, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31810] Another function of VGAM824 is therefore inhibition of KIAA1432 (Accession XM\_039698). Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1432. Stromal Antigen 2 (STAG2, Accession XM\_047285) is another VGAM824 host target gene. STAG2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STAG2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of STAG2 BINDING SITE, designated SEQ ID:34927, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31811] Another function of VGAM824 is therefore inhibition of Stromal Antigen 2 (STAG2, Accession XM\_047285). Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAG2. LOC255654 (Accession XM\_173036) is another VGAM824 host target gene. LOC255654 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC255654, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255654 BINDING SITE, designated SEQ ID:46301, to the nucleotide sequence of VGAM824 RNA, herein designated VGAM RNA, also designated SEQ ID:3535.

[31812] Another function of VGAM824 is therefore inhibition of LOC255654 (Accession XM\_173036). Accordingly, utilities of VGAM824 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255654. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 825 (VGAM825) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31813] VGAM825 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM825 was detected is described hereinabove with reference to Figs. 1–8.

[31814] VGAM825 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus. VGAM825 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31815] VGAM825 gene encodes a VGAM825 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM825 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM825 precursor RNA is designated SEQ ID:811, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:811 is

located at position 80642 relative to the genome of Monkeypox Virus.

[31816] VGAM825 precursor RNA folds onto itself, forming VGAM825 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31817] An enzyme complex designated DICER COMPLEX, `dices` the VGAM825 folded precursor RNA into VGAM825 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 77%) nucleotide sequence of VGAM825 RNA is designated SEQ ID:3536, and is provided hereinbelow with reference to the sequence listing part.

[31818] VGAM825 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM825 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM825 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[31819] VGAM825 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM825 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM825 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM825 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM825 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31820] The complementary binding of VGAM825 RNA, herein designated VGAM RNA, to host target binding sites on VGAM825 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM825 host target RNA into VGAM825 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31821] It is appreciated that VGAM825 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM825 host target genes. The mRNA of each one of this plurality of VGAM825 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM825 RNA, herein designated VGAM RNA, and which when bound by VGAM825 RNA causes inhibition of translation of respective one or more VGAM825



host target proteins.

[31822] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM825 gene, herein designated VGAM GENE, on one or more VGAM825 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31823] It is yet further appreciated that a function of VGAM825 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM825 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific

functions, and accordingly utilities, of VGAM825 correlate with, and may be deduced from, the identity of the host target genes which VGAM825 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31824] Nucleotide sequences of the VGAM825 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM825 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM825 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM825 are further described hereinbelow with reference to Table 1.

[31825] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM825 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM825 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31826] As mentioned hereinabove with reference to Fig. 1, a function of VGAM825 gene, herein designated VGAM is inhibition of expression of VGAM825 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM825 correlate with, and may be deduced from, the identity of the target genes which VGAM825 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31827] Integrin, Alpha 6 (ITGA6, Accession NM\_000210) is a VGAM825 host target gene. ITGA6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGA6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGA6 BINDING SITE, designated SEQ ID:5702, to the nucleotide sequence of VGAM825 RNA, herein designated VGAM RNA, also designated SEQ ID:3536.

[31828] A function of VGAM825 is therefore inhibition of Integrin, Alpha 6 (ITGA6, Accession NM\_000210). Accordingly, utilities of VGAM825 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGA6. Mitogen-activated Protein Kinase 3 (MAPK3, Accession XM\_055766) is another VGAM825 host target gene. MAPK3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAPK3, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPK3 BINDING SITE, designated SEQ ID:36322, to the nucleotide sequence of VGAM825 RNA, herein designated VGAM RNA, also designated SEQ ID:3536.

[31829] Another function of VGAM825 is therefore inhibition of Mitogen-activated Protein Kinase 3 (MAPK3, Accession XM\_055766), a gene which phosphorylates microtubule-associated protein-2, myelin basic protein, and elk-1; may promote entry into the cell cycle. Accordingly, utilities of VGAM825 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPK3. The function of MAPK3 has been established by previous studies. Experience-dependent plasticity in the developing visual cortex depends on electrical activity and molecular signals involved in stabilization or removal of inputs. ERK1 and ERK2 (MAPK1) activation in the cortex is regulated by both factors. Di Cristo et al. (2001) demonstrated that 2 different inhibitors of the ERK pathway suppress the induction of 2 forms of long-term potentiation in rat cortical slices and that their intracortical administration to monocularly deprived rats prevents the shift in ocular

dominance towards the nondeprived eye. Di Cristo et al. (2001) concluded that the ERK pathway is necessary for experience-dependent plasticity and for long-term potentiation of synaptic transmission in the developing visual cortex. Forcet et al. (2002) showed that in embryonic kidney cells expressing full-length, but not cytoplasmic domain-truncated, DCC (OMIM Ref. No. 120470), NTN1 (OMIM Ref. No. 601614) causes increased transient phosphorylation and activity of ERK1 and ERK2 (OMIM Ref. No. 176948), but not of JNK1 (OMIM Ref. No. 601158), JNK2 (OMIM Ref. No. 602896), or p38 (MAPK14; 600289). This phosphorylation was mediated by MEK1 (MAP2K1; 176872) and/or MEK2 (MAP2K2; 601263). NTN1 also activated the transcription factor ELK1 (OMIM Ref. No. 311040) and serum response element-regulated gene expression. Immunoprecipitation analysis showed interaction of full-length DCC with MEK1/2 in the presence or absence of NTN1. Forcet et al. (2002) showed that activation of Dcc by Ntn1 in rat embryonic day-13 dorsal spinal cord stimulates and is required for the outgrowth of commissural axons and Erk1/2 activation. Immunohistochemical analysis demonstrated expression of activated Erk1/2 in embryonic commissural axons, and this expression was

diminished in Dcc or Ntn1 knockout animals. Forcet et al. (2002) concluded that the MAPK pathway is involved in responses to NTN1 and proposed that ERK activation affects axonal growth by phosphorylation of microtubule-associated proteins and neurofilaments. Animal model experiments lend further support to the function of MAPK3. Pages et al. (1999) generated p44 Mapk (Erk1)-deficient mice by homologous recombination in embryonic stem cells. The p44 Mapk were viable, fertile, and of normal size. Thus, Pages et al. (1999) concluded that p44 Mapk is apparently dispensable and that p42 Mapk (Erk2) may compensate for its loss. However, in p44 Mapk  $-/-$  mice, thymocyte maturation beyond the CD4<sup>+</sup>CD8<sup>+</sup> stage was reduced by half, with a similar diminution in the thymocyte subpopulation expressing high levels of T cell receptor (CD3-high). In p44 Mapk  $-/-$  thymocytes, proliferation in response to activation with a monoclonal antibody to the T cell receptor in the presence of phorbol myristate acetate was severely reduced even though activation of p42 Mapk was more sustained in these cells. Thus, Pages et al. (1999) concluded that p44 Mapk apparently has a specific role in thymocyte development.

[31830] It is appreciated that the abovementioned animal model

for MAPK3 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[31831] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31832] Pages, G.; Guerin, S.; Grall, D.; Bonino, F.; Smith, A.; Anjuere, F.; Auberger, P.; Pouyssegur, J. : Defective thymocyte maturation in p44 MAP kinase (Erk 1) knockout mice. Science 286: 1374–1378, 1999. ; and

[31833] Forcet, C.; Stein, E.; Pays, L.; Corset, V.; Llambi, F.; Tessier-Lavigne, M.; Mehlen, P. : Netrin-1-mediated axon outgrowth requires deleted in colorectal cancer-dependent MAPK activation.

[31834] Further studies establishing the function and utilities of MAPK3 are found in John Hopkins OMIM database record ID 601795, and in cited publications numbered 5785–1533, 6235, 623 and 6237 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ12903 (Accession NM\_022753) is another VGAM825 host target gene. FLJ12903 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ12903, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12903 BINDING SITE, designated SEQ ID:22982, to the nucleotide sequence of VGAM825 RNA, herein designated VGAM RNA, also designated SEQ ID:3536.

[31835] Another function of VGAM825 is therefore inhibition of FLJ12903 (Accession NM\_022753). Accordingly, utilities of VGAM825 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12903. UCH37 (Accession NM\_015984) is another VGAM825 host target gene. UCH37 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UCH37, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UCH37 BINDING SITE, designated SEQ ID:18080, to the nucleotide sequence of VGAM825 RNA, herein designated VGAM RNA, also designated SEQ ID:3536.

[31836] Another function of VGAM825 is therefore inhibition of UCH37 (Accession NM\_015984). Accordingly, utilities of VGAM825 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with UCH37. LOC132321 (Accession XM\_059585) is another VGAM825 host target gene. LOC132321 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC132321, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC132321 BINDING SITE, designated SEQ ID:37026, to the nucleotide sequence of VGAM825 RNA, herein designated VGAM RNA, also designated SEQ ID:3536.

[31837] Another function of VGAM825 is therefore inhibition of LOC132321 (Accession XM\_059585). Accordingly, utilities of VGAM825 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC132321. LOC222066 (Accession XM\_166582) is another VGAM825 host target gene. LOC222066 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222066, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222066 BINDING SITE, designated SEQ ID:44554, to

the nucleotide sequence of VGAM825 RNA, herein designated VGAM RNA, also designated SEQ ID:3536.

[31838] Another function of VGAM825 is therefore inhibition of LOC222066 (Accession XM\_166582). Accordingly, utilities of VGAM825 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222066. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 826 (VGAM826) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31839] VGAM826 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM826 was detected is described hereinabove with reference to Figs. 1–8.

[31840] VGAM826 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Herpesvirus 4. VGAM826 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31841] VGAM826 gene encodes a VGAM826 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM826 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM826 precursor RNA is designated SEQ ID:812, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:812 is located at position 92205 relative to the genome of Bovine Herpesvirus 4.

[31842] VGAM826 precursor RNA folds onto itself, forming VGAM826 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31843] An enzyme complex designated DICER COMPLEX, `dices` the VGAM826 folded precursor RNA into VGAM826 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM826 RNA is designated SEQ ID:3537, and is provided hereinbelow with reference to the sequence listing part.

[31844] VGAM826 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM826 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM826 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[31845] VGAM826 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM826 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM826 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM826 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM826 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31846] The complementary binding of VGAM826 RNA, herein designated VGAM RNA, to host target binding sites on VGAM826 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM826 host target RNA into VGAM826 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31847] It is appreciated that VGAM826 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM826 host target genes. The mRNA of each one of this plurality of VGAM826 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM826 RNA, herein designated VGAM RNA, and which when bound by VGAM826 RNA causes inhibition of translation of respective one or more VGAM826 host target proteins.

[31848] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM826 gene, herein designated VGAM GENE, on one or more VGAM826 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[31849] It is yet further appreciated that a function of VGAM826 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of viral infection by Bovine Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM826 correlate with, and may be deduced from, the identity of the host target genes which VGAM826 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31850] Nucleotide sequences of the VGAM826 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM826 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM826 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM826 are further described hereinbelow with reference to Table 1.

[31851] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM826 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM826 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31852] As mentioned hereinabove with reference to Fig. 1, a function of VGAM826 gene, herein designated VGAM is inhibition of expression of VGAM826 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM826 correlate with, and may be deduced from, the identity of the target genes which VGAM826 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31853] Dihydrofolate Reductase (DHFR, Accession NM\_000791) is a VGAM826 host target gene. DHFR BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DHFR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DHFR BINDING SITE, designated SEQ ID:6447, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31854] A function of VGAM826 is therefore inhibition of Dihydrofolate Reductase (DHFR, Accession NM\_000791), a gene



which converts dihydrofolate into tetrahydrofolate. Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DHFR. The function of DHFR has been established by previous studies. Dihydrofolate reductase (EC 1.5.1.3) converts dihydrofolate into tetrahydrofolate, a methyl group shuttle required for the de novo synthesis of purines, thymidylic acid, and certain amino acids. DHFR is inhibited by methotrexate (MTX), a folate analog used as an antineoplastic and immunosuppressive agent. From comparisons of eukaryotic gene sequences and protein sequences of homologous enzymes from bacterial and mammalian organisms, Craik et al. (1983) noted that intron-exon junctions often coincide with variable surface loops of the protein structure. Proteins studied included DHFR, trypsin, and chymotrypsin. They pointed out that altered surface structures can account for functional differences among the members of a family, e.g., the serine proteases. 'Sliding' of the intron-exon junctions may constitute a mechanism for generating length polymorphisms and divergent sequences. Different function can thus be achieved without disrupting the stability of the protein core. DNA sequence amplification is one of the most fre-

quent manifestations of genomic instability in human tumors. In most human tumor cells, amplified DNA sequences are borne on unstable, extrachromosomal double minutes (DMs). Singer et al. (2000) isolated a large number of independent methotrexate-resistant human cell lines, all of which contained DHFR-bearing DMs. All but one of these also had suffered partial or complete loss of one of the parental DHFR-bearing chromosomes. Cells in a few populations displayed what could be transient intermediates in the amplification process, including an initial homogeneously staining chromosome region (HSR), its subsequent breakage, the appearance of DHFR-containing fragments, and, finally, DMs. The studies suggested that both HSRs and DMs are initiated by chromosome breaks, but that cell types differ in how the extra sequences ultimately are processed and/or maintained.

[31855] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31856] Singer, M. J.; Mesner, L. D.; Friedman, C. L.; Trask, B. J.; Hamlin, J. L. : Amplification of the human dihydrofolate reductase gene via double minutes is initiated by chromosome breaks. Proc. Nat. Acad. Sci. 97: 7921–7926, 2000. ;

and

[31857] Craik, C. S.; Rutter, W. J.; Fletterick, R. : Splice junctions: association with variation in protein structure. Science 220: 1125–1129, 1983.

[31858] Further studies establishing the function and utilities of DHFR are found in John Hopkins OMIM database record ID 126060, and in cited publications numbered 3985–4002 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Heat Shock 70kDa Protein 1B (HSPA1B, Accession NM\_005346) is another VGAM826 host target gene. HSPA1B BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by HSPA1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPA1B BINDING SITE, designated SEQ ID:11819, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31859] Another function of VGAM826 is therefore inhibition of Heat Shock 70kDa Protein 1B (HSPA1B, Accession NM\_005346), a gene which stabilizes preexistent proteins against aggregation and mediate the folding of newly

translated polypeptides in the cytosol as well as within organelles. Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPA1B. The function of HSPA1B has been established by previous studies. Heat-shock proteins, or stress proteins, are expressed in response to heat shock and a variety of other stress stimuli including oxidative free radicals and toxic metal ions. The human HSP70, or HSPA, multigene family encodes several highly conserved 70-kD proteins with structural and functional properties in common, but which vary in their inducibility in response to metabolic stress. Sargent et al. (1989) identified a duplicated HSP70 locus in the class III region of the major histocompatibility complex on 6p21.3. These loci, HSP70-1 (HSPA1A; 140550) and HSP70-2 (OMIM Ref. No. HSPA1B), are 12 kb apart and lie 92 kb telomeric to the C2 gene (see OMIM Ref. No. 217000). Milner and Campbell (1990) determined that the HSP70-2 gene, like HSP70-1, lacks introns. The HSP70-1 and -2 coding sequences, which differ by 8 bp that do not alter the derived amino acid sequence, encode identical 641-amino acid proteins; the 3-prime untranslated regions of these genes are completely divergent. Northern

blot analysis of HeLa cell RNA detected an approximately 2.4-kb HSP70-2 transcript that was expressed at elevated levels following heat shock. Milner and Campbell (1992) investigated the presence of sequence variation in the HSP70-2 gene among different HLA haplotypes. They found only very limited sequence variation, which did not result in amino acid substitutions.

[31860] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31861] Milner, C. M.; Campbell, R. D. : Structure and expression of the three MHC-linked HSP70 genes. Immunogenetics 32: 242-251, 1990. ; and

[31862] Milner, C. M.; Campbell, R. D. : Polymorphic analysis of the three MHC-linked HSP70 genes. Immunogenetics 36: 357-362, 1992.

[31863] Further studies establishing the function and utilities of HSPA1B are found in John Hopkins OMIM database record ID 603012, and in cited publications numbered 1161 and 11611 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 1 (p85 alpha) (PIK3R1, Accession XM\_043865)

is another VGAM826 host target gene. PIK3R1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIK3R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIK3R1 BINDING SITE, designated SEQ ID:34040, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31864] Another function of VGAM826 is therefore inhibition of Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 1 (p85 alpha) (PIK3R1, Accession XM\_043865), a gene which acts as an adapter, for the insulin-stimulated increase in glucose uptake and glycogen synthesis. Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIK3R1. The function of PIK3R1 has been established by previous studies. Phosphatidylinositol 3-kinase (PIK3) activity is implicated in diverse cellular responses triggered by mammalian cell surface receptors. Stoyanov et al. (1995) noted that receptors with tyrosine kinase activity recruit heterodimeric PIK3 kinases composed of a p110 catalytic subunit and a p85 adaptor subunit (OMIM

Ref. No. 171833). Stoyanov et al. (1995) screened a human bone marrow cDNA library with primers based on the sequences of yeast and bovine PIK3 p110 subunits. They isolated a human cDNA for a novel p110 subunit, which they termed p110-gamma. The cDNA encodes a predicted 120-kD, 1,050-amino acid polypeptide with 36% identity to human p110-alpha (OMIM Ref. No. 171834). The 5.3-kb p110-alpha transcript was detectable by Northern blot in human pancreas, skeletal muscle, liver, and heart. Stoyanov et al. (1995) found that recombinant p110-gamma did not interact with the p85 subunit in vivo, in contrast to recombinant p110-alpha. The transducin G protein subunits G-beta(t) (OMIM Ref. No. 189974)/G-gamma(t) (OMIM Ref. No. 189970) did, however, activate p110-gamma in vitro, and the stimulation was suppressed by G-alpha(t)-GDP (OMIM Ref. No. 139330); G-alpha(t)-GDP could stimulate p110-gamma only in the presence of AlF(4-). In contrast, the p85-dependent p110-alpha was not similarly affected by the G protein subunits. Stoyanov et al. (1995) speculated that the p110-gamma isotype may link signaling through G protein-coupled receptors and generate phosphoinositide second messengers phosphorylated in the D-3 posi-

tion Animal model experiments lend further support to the function of PI3K. Phosphoinositide 3-kinase (PI3K) activation is implicated in many responses, including fibroblast growth, transformation, survival, and chemotaxis. Although PI3K is activated by several agents that stimulate T and B cells, the role of PI3K in lymphocyte function remained to be clarified. Fruman et al. (1999) disrupted the mouse gene encoding the PI3K adaptor subunit p85- $\alpha$  and its splice variants p55- $\alpha$  and p50- $\alpha$ . Most mice homozygous for disruption for all 3 variants died within days after birth. Lymphocyte development and function were studied with the use of the RAG2-deficient blastocyst complementation system. Chimeric mice had reduced numbers of peripheral mature B cells and decreased serum immunoglobulin. The B cells that developed had diminished proliferative responses to antibody to immunoglobulin M, antibody to CD40, and lipopolysaccharide stimulation, as well as decreased survival after incubation with interleukin-4. In contrast, T-cell development and proliferation were normal. This phenotype was similar to defects observed in mice lacking the tyrosine kinase Btk and in patients with Bruton X-linked agammaglobulinemia (300300



[31865] It is appreciated that the abovementioned animal model for PIK3R1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[31866] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31867] Fruman, D. A.; Snapper, S. B.; Yballe, C. M.; Davidson, L.; Yu, J. Y.; Alt, F. W.; Cantley, L. C. : Impaired B cell development and proliferation in absence of phosphoinositide 3-kinase p85-alpha. Science 283: 393-397, 1999. ; and

[31868] Simoncini, T.; Hafezi-Moghadam, A.; Brazil, D. P.; Ley, K.; Chin, W. W.; Liao, J. K. : Interaction of oestrogen receptor with the regulatory subunit of phosphatidylinositol-3-OH kinase. N.

[31869] Further studies establishing the function and utilities of PIK3R1 are found in John Hopkins OMIM database record ID 171833, and in cited publications numbered 3521-3522, 3834-3837, 1085 and 3839-3842 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger Protein 80 (pT17) (ZNF80, Accession NM\_007136) is another VGAM826 host target gene. ZNF80 BINDING SITE is HOST

TARGET binding site found in the 5` untranslated region of mRNA encoded by ZNF80, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF80 BINDING SITE, designated SEQ ID:13986, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31870] Another function of VGAM826 is therefore inhibition of Zinc Finger Protein 80 (pT17) (ZNF80, Accession NM\_007136). Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF80. KIAA0562 (Accession NM\_014704) is another VGAM826 host target gene. KIAA0562 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0562, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0562 BINDING SITE, designated SEQ ID:16244, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31871] Another function of VGAM826 is therefore inhibition of KIAA0562 (Accession NM\_014704). Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0562. KIAA1219 (Accession XM\_028835) is another VGAM826 host target gene. KIAA1219 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1219, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1219 BINDING SITE, designated SEQ ID:30761, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31872] Another function of VGAM826 is therefore inhibition of KIAA1219 (Accession XM\_028835). Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1219. Organic Cationic Transporter-like 3 (ORCTL3, Accession NM\_004256) is another VGAM826 host target gene. ORCTL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ORCTL3, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ORCTL3 BINDING SITE, designated SEQ ID:10443, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31873] Another function of VGAM826 is therefore inhibition of Organic Cationic Transporter-like 3 (ORCTL3, Accession NM\_004256). Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ORCTL3. Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654) is another VGAM826 host target gene. SDC3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SDC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDC3 BINDING SITE, designated SEQ ID:16079, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31874] Another function of VGAM826 is therefore inhibition of Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654).

Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDC3. LOC115219 (Accession XM\_055499) is another VGAM826 host target gene.

LOC115219 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC115219, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115219 BINDING SITE, designated SEQ ID:36276, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31875] Another function of VGAM826 is therefore inhibition of LOC115219 (Accession XM\_055499). Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115219. LOC223073 (Accession XM\_170293) is another VGAM826 host target gene. LOC223073 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC223073, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC223073 BINDING SITE, designated SEQ ID:45317, to the nucleotide sequence of VGAM826 RNA, herein designated VGAM RNA, also designated SEQ ID:3537.

[31876] Another function of VGAM826 is therefore inhibition of LOC223073 (Accession XM\_170293). Accordingly, utilities of VGAM826 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC223073. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 827 (VGAM827) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31877] VGAM827 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM827 was detected is described hereinabove with reference to Figs. 1–8.

[31878] VGAM827 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Bovine Herpesvirus 4. VGAM827 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[31879] VGAM827 gene encodes a VGAM827 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM827 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM827 precursor RNA is designated SEQ ID:813, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:813 is located at position 90686 relative to the genome of Bovine Herpesvirus 4.

[31880] VGAM827 precursor RNA folds onto itself, forming VGAM827 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31881] An enzyme complex designated DICER COMPLEX, `dices` the VGAM827 folded precursor RNA into VGAM827 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 73%) nucleotide sequence of VGAM827 RNA is designated SEQ ID:3538, and is provided hereinbelow with reference to the sequence listing part.

[31882] VGAM827 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM827 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM827 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[31883] VGAM827 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM827 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM827 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-



quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM827 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM827 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31884] The complementary binding of VGAM827 RNA, herein designated VGAM RNA, to host target binding sites on VGAM827 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM827 host target RNA into VGAM827 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31885] It is appreciated that VGAM827 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM827 host target genes. The mRNA of each one of this plurality of VGAM827 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM827 RNA, herein designated VGAM RNA, and which when bound by VGAM827 RNA causes inhibition of translation of respective one or more VGAM827 host target proteins.

[31886] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM827 gene, herein designated VGAM GENE, on one or more VGAM827 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31887] It is yet further appreciated that a function of VGAM827 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of viral infection by Bovine Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM827 correlate with, and may be deduced from, the identity of the host target genes which VGAM827 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31888] Nucleotide sequences of the VGAM827 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM827 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM827 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM827 are further described hereinbelow with reference to Table 1.

[31889] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM827 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM827 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[31890] As mentioned hereinabove with reference to Fig. 1, a function of VGAM827 gene, herein designated VGAM is inhibition of expression of VGAM827 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM827 correlate with, and may be deduced from, the identity of the target genes which VGAM827 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31891] ATPase, H<sup>+</sup> Transporting, Lysosomal 70kDa, V1 Subunit A, Isoform 1 (ATP6V1A1, Accession NM\_001690) is a VGAM827 host target gene. ATP6V1A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP6V1A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP6V1A1 BINDING SITE, designated SEQ ID:7412, to the nucleotide sequence of VGAM827 RNA, herein designated

VGAM RNA, also designated SEQ ID:3538.

[31892] A function of VGAM827 is therefore inhibition of ATPase, H<sup>+</sup> Transporting, Lysosomal 70kDa, V1 Subunit A, Iso-form 1 (ATP6V1A1, Accession NM\_001690), a gene which is responsible for acidifying a variety of intracellular compartments in eukaryotic cells. Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP6V1A1. The function of ATP6V1A1 has been established by previous studies. Van Hille et al. (1993) cloned a partial cDNA clone for an A subunit isoform, which they designated VA68, from a human osteoclastoma tumor cDNA library by PCR using degenerate primers based on the bovine sequence. They obtained a full-length clone from a genomic library. The deduced 617-amino acid protein has a predicted molecular mass of about 68 kD and shows 99% sequence identity with the bovine brain subunit A. Northern blot analysis revealed ubiquitous expression of a major 4.8-kb band and a minor 3.4-kb band. They also identified a variant, which they designated HO68, encoding a 615-amino acid protein. By RNase protection assays and in situ hybridization, van Hille et al. (1995) determined that expression of the HO68

variant was specific to the osteoclastoma originally used to construct the cDNA library.

[31893] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31894] van Hille, B.; Richener, H.; Evans, D. B.; Green, J. R.; Bilbe, G. : Identification of two subunit A isoforms of the vacuolar H(+)-ATPase in human osteoclastoma. J. Biol. Chem. 268: 7075-7080, 1993. ; and

[31895] van Hille, B.; Richener, H.; Green, J. R.; Bilbe, G. : The ubiquitous VA68 isoform of subunit A of the vacuolar H(+)-ATPase is highly expressed in human osteoclasts. Biochem. Biophys.

[31896] Further studies establishing the function and utilities of ATP6V1A1 are found in John Hopkins OMIM database record ID 607027, and in cited publications numbered 5382-5383 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Dual-specificity tyrosine-(Y)-phosphorylation Regulated Kinase 1A (DYRK1A, Accession NM\_130436) is another VGAM827 host target gene. DYRK1A BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DYRK1A, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DYRK1A BINDING SITE, designated SEQ ID:28192, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31897] Another function of VGAM827 is therefore inhibition of Dual-specificity tyrosine-(Y)-phosphorylation Regulated Kinase 1A (DYRK1A, Accession NM\_130436), a gene which regulates cell proliferation and may be involved in brain development . Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DYRK1A. The function of DYRK1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM42.Ectonucleoside Triphosphate Diphosphohydrolase 6 (putative function) (ENTPD6, Accession NM\_001247) is another VGAM827 host target gene. ENTPD6 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ENTPD6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of ENTPD6 BINDING SITE, designated SEQ ID:6920, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31898] Another function of VGAM827 is therefore inhibition of Ectonucleoside Triphosphate Diphosphohydrolase 6 (putative function) (ENTPD6, Accession NM\_001247), a gene which might support glycosylation reactions in the golgi apparatus and, when released from cells, might catalyze the hydrolysis of extracellular nucleotides. Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ENTPD6. The function of ENTPD6 has been established by previous studies. Extracellular nucleotides serve as signaling molecules in many extracellular activities. The catabolism of extracellular nucleotides is mediated by several types of ectonucleotidases, including the divalent cation-dependent E-type nucleotidases (NTPases). The E-type NTPases include ectoapyrases, such as CD39 (OMIM Ref. No. 601752), which show a significant rate of ADP hydrolysis compared to ATP hydrolysis. NTPases are characterized by the presence of 4 motifs



known as apyrase-conserved regions (ACRs). Chadwick et al. (1998) identified cDNAs encoding a mouse NTPase, symbolized MNTPase. By searching an EST database for sequences similar to that of MNTPase, Chadwick and Frischauf (1998) identified cDNAs corresponding to 2 human genes, CD39L2 and CD39L4 (OMIM Ref. No. 603162). The predicted 484-amino acid CD39L2 protein contains all 4 ACRs, a single N-terminal transmembrane segment, and a large extracellular C-terminal domain. Northern blot analysis revealed that CD39L2 was expressed as a major 2.6-kb and minor 4.4-kb mRNA in all tissues tested. Homology searches yielded ESTs likely to represent the mouse *cd39l2* gene. By PCR and sequence analysis of cDNA libraries, and by Northern blot analysis, Yeung et al. (2000) detected CD39L2 predominantly in heart, with very low or no expression in other tissues. In situ hybridization analysis revealed expression distinctively in cardiac muscle and capillary endothelial cells. A larger variant, resulting from a 43-bp insertion in exon 14, was detected in fetal brain. Western blot analysis of cells expressing recombinant CD39L2 detected expression of an approximately 60-kD protein triplet primarily in the secreted fraction but also on membranes. Glycosidase treatment

reduced the size of the protein to 57 kD, still greater than the predicted 53 kD, suggesting additional posttranslational modifications. Brefeldin A treatment decreased the secretion of CD39L2. Flow cytometric analysis demonstrated expression on the extracellular membrane. Functional analysis showed that, like CD39L4, CD39L2 preferentially hydrolyzes nucleotide diphosphates rather than triphosphates. This hydrolysis is enhanced in the presence of magnesium or calcium. However, in contrast to CD39, calcium excess fails to inhibit CD39L2-mediated adenosine diphosphatase activity. On the basis of structural and biochemical features, Yeung et al. (2000) concluded that CD39L2 and CD39L4 are in a separate subclass, defined by the presence of only 1 N-terminal hydrophobic transmembrane domain, from CD39, CD39L1 (OMIM Ref. No. 602012), and CD39L3 (OMIM Ref. No. 603161), which have an N-terminal and a C-terminal transmembrane domain. By analysis of radiation hybrid and somatic cell hybrid panels, Chadwick and Frischauf (1998) mapped the CD39L2 gene to 20q11.2.

[31899] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [31900] Chadwick, B. P.; Williamson, J.; Sheer, D.; Frischauf, A.-M. : cDNA cloning and chromosomal mapping of a mouse gene with homology to NTPases. *Mammalian Genome* 9: 162–164, 1998. ; and
- [31901] Yeung, G.; Mulero, J. J.; McGowan, D. W.; Bajwa, S. S.; Ford, J. E. : CD39L2, a gene encoding a human nucleoside diphosphatase, predominantly expressed in the heart. *Biochemistry* 39: 12.
- [31902] Further studies establishing the function and utilities of ENTPD6 are found in John Hopkins OMIM database record ID 603160, and in cited publications numbered 6232–2429 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fibronectin Leucine Rich Transmembrane Protein 1 (FLRT1, Accession XM\_006111) is another VGAM827 host target gene. FLRT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLRT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLRT1 BINDING SITE, designated SEQ ID:29992, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ

ID:3538.

[31903] Another function of VGAM827 is therefore inhibition of Fibronectin Leucine Rich Transmembrane Protein 1 (FLRT1, Accession XM\_006111). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLRT1. Glycoprotein M6A (GPM6A, Accession NM\_005277) is another VGAM827 host target gene. GPM6A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPM6A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPM6A BINDING SITE, designated SEQ ID:11782, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31904] Another function of VGAM827 is therefore inhibition of Glycoprotein M6A (GPM6A, Accession NM\_005277), a gene which may play a role in neuronal development. Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPM6A. The function of GPM6A and its association with various diseases and clinical conditions, has

been established by previous studies, as described herein above with reference to VGAM326. Integrin, Alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor) (ITGA2, Accession NM\_002203) is another VGAM827 host target gene. ITGA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGA2 BINDING SITE, designated SEQ ID:7963, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31905] Another function of VGAM827 is therefore inhibition of Integrin, Alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor) (ITGA2, Accession NM\_002203), a gene which has roles in blood clotting and angiogenesis, acts as a collagen and laminin receptor. Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGA2. The function of ITGA2 has been established by previous studies. By screening a uterus cDNA library with an integrin-like cDNA fragment isolated from a fetal myoblast

cDNA library, Velling et al. (1999) obtained a full-length cDNA sequence encoding integrin alpha-11. ITGA11 encodes a deduced 1,188-amino acid protein, including a 22-amino acid signal peptide. The mature 1,166-amino acid protein contains a 23-amino acid transmembrane region and a 24-amino acid cytoplasmic tail. It differs from most other integrin alpha chains in that the cytoplasmic tail contains the sequence GFFRS instead of the conserved GFFKR sequence. The extracellular domain contains 7 FG-GAP repeats with an I domain of 195 amino acids between repeats 2 and 3 that includes a conserved metal ion-dependent adhesion site motif. Twenty cysteines are located in the extracellular domain and there are 16 potential N-glycosylation sites. ITGA11 is 42%, 37%, and 35% identical with I domain alpha-integrins ITGA10 (OMIM Ref. No. 604042), ITGA1 (OMIM Ref. No. 192968), and ITGA2 (OMIM Ref. No. 192974), respectively. Northern blot analysis revealed expression of an approximately 5.5-kb ITGA11 transcript. Expression was highest in uterus, strong in heart, intermediate in skeletal muscle, stomach, small intestine, bladder, prostate, and colon, and low in nonmuscle tissues such as pancreas, kidney, and placenta. The authors found that, in contrast, ITGA1 is not

expressed in the uterus. Immunoprecipitation studies and SDS-PAGE analysis showed that ITGA11 encodes a 145-kD protein, intermediate in size between ITGA2 or ITGA10 and ITGA1; the authors suggested that the difference is probably due to differential glycosylation. Like other I domain-containing integrins, ITGA11 binds to collagen. By sequence analysis, Lehnert et al. (1999) found that the deduced ITGA11 protein contains an I domain of 207 amino acids and 15 N-glycosylation sites in a mature protein of 1167 amino acids. By FISH, Velling et al. (1999) mapped the ITGA11 gene to chromosome 15q23. By somatic cell hybrid analysis and FISH, Lehnert et al. (1999) mapped the gene to 15q22.3-q23.

[31906] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31907] Lehnert, K.; Ni, J.; Leung, E.; Gough, S. M.; Weaver, A.; Yao, W.-P.; Liu, D.; Wang, S.-X.; Morris, C. M.; Krissansen, G. W. : Cloning, sequence analysis, and chromosomal localization of the novel human integrin alpha-11 subunit (ITGA11). *Genomics* 60: 179-187, 1999. ; and

[31908] Velling, T.; Kusche-Gullberg, M.; Sejersen, T.; Gullberg, D. : cDNA cloning and chromosomal localization of human

alpha-11 integrin: a collagen-binding, I domain-containing, beta-1-asso.

[31909] Further studies establishing the function and utilities of ITGA2 are found in John Hopkins OMIM database record ID 192974, and in cited publications numbered 6052-6053, 6381, 10003-1001 and 3351 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Mesenchyme Homeo Box 2 (growth arrest-specific homeo box) (MEOX2, Accession NM\_005924) is another VGAM827 host target gene. MEOX2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MEOX2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEOX2 BINDING SITE, designated SEQ ID:12551, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31910] Another function of VGAM827 is therefore inhibition of Mesenchyme Homeo Box 2 (growth arrest-specific homeo box) (MEOX2, Accession NM\_005924), a gene which roles in mesoderm induction and, somitogenesis, and myogenic



and sclerotomal differentiation. Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEOX2. The function of MEOX2 has been established by previous studies. Candia et al. (1992) and Gorski et al. (1993) isolated and studied the murine Mox2 gene, which belongs to a family of nonclustered, diverged homeo box genes. In situ hybridization analysis during murine embryogenesis indicated that the Mox2 gene is expressed in a wide range of mesodermal structures, including somites and vertebrae, the developing limbs, groups of muscles of the head, and the developing palate. These findings suggested that mutations in the human homolog of the Mox2 gene may be involved in craniofacial and/or skeletal abnormalities in the human. They isolated and characterized cDNA clones for the human homolog, which they termed MOX2, and found that it contains all of the characteristic features of Mox2 proteins of other vertebrate species, namely the homeo box, the polyhistidine stretch, and a number of potential serine/threonine phosphorylation sites. The homeodomain of the Mox2 protein is identical to that in all other vertebrate species studied to that time (rodents and amphibians). By fluorescence in situ hy-

bridization, Grigoriou et al. (1995) mapped the human MEOX2 gene to 7p22.1–p21.3. This is the region where the Saethre–Chotzen syndrome (OMIM Ref. No. 101400) maps, thus it became a candidate for the site of the mutation in that disorder. Mankoo et al. (1999) generated mice homozygous for a null mutation of Mox2 by targeted disruption. Mox2  $-/-$  mice have a developmental defect of the limb musculature characterized by an overall reduction in muscle mass and elimination of specific muscles. Mox2 is not needed for the migration of myogenic precursors into the limb bud, but it is essential for normal appendicular muscle formation and for the normal regulation of myogenic genes, as demonstrated by the down-regulation of Pax3 (OMIM Ref. No. 600535) and Myf5 (OMIM Ref. No. 159990) but not MyoD (OMIM Ref. No. 159970) in Mox2-deficient limb buds. Mankoo et al. (1999) concluded that MOX2 homeoprotein is an important regulator of vertebrate limb myogenesis.

[31911] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31912] Candia, A. F.; Hu, J.; Crosby, J.; Lalley, P. A.; Noden, D.; Nadeau, J. H.; Wright, C. V. E. : Mox–1 and Mox–2 define a

novel homeobox gene subfamily and are differentially expressed during early mesodermal patterning in mouse embryos. Development 116: 1123–1136, 1992. ; and

[31913] Mankoo, B. S.; Collins, N. S.; Ashby, P.; Grigorieva, E.; Pevny, L. H.; Candia, A.; Wright, C. V. E.; Rigby, P. W. J.; Pachnis, V. : Mox2 is a component of the genetic hierarchy contro.

[31914] Further studies establishing the function and utilities of MEOX2 are found in John Hopkins OMIM database record ID 600535, and in cited publications numbered 7679–7683 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Neurocalcin Delta (NCALD, Accession NM\_032041) is another VGAM827 host target gene. NCALD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCALD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCALD BINDING SITE, designated SEQ ID:25749, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31915] Another function of VGAM827 is therefore inhibition of

Neurocalcin Delta (NCALD, Accession NM\_032041). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCALD. Neuralized-like (Drosophila) (NEURL, Accession NM\_004210) is another VGAM827 host target gene. NEURL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEURL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEURL BINDING SITE, designated SEQ ID:10412, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31916] Another function of VGAM827 is therefore inhibition of Neuralized-like (Drosophila) (NEURL, Accession NM\_004210). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEURL. Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 3 (p55, gamma) (PIK3R3, Accession XM\_027982) is another VGAM827 host target gene. PIK3R3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA en-

coded by PIK3R3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIK3R3 BINDING SITE, designated SEQ ID:30610, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31917] Another function of VGAM827 is therefore inhibition of Phosphoinositide-3-kinase, Regulatory Subunit, Polypeptide 3 (p55, gamma) (PIK3R3, Accession XM\_027982). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIK3R3. RAB3B, Member RAS Oncogene Family (RAB3B, Accession NM\_002867) is another VGAM827 host target gene. RAB3B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB3B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB3B BINDING SITE, designated SEQ ID:8772, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31918] Another function of VGAM827 is therefore inhibition of RAB3B, Member RAS Oncogene Family (RAB3B, Accession NM\_002867). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB3B. Ring Finger Protein 14 (RNF14, Accession NM\_004290) is another VGAM827 host target gene. RNF14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNF14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF14 BINDING SITE, designated SEQ ID:10506, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31919] Another function of VGAM827 is therefore inhibition of Ring Finger Protein 14 (RNF14, Accession NM\_004290), a gene which associates with the androgen receptor (AR); functions as a transcriptional coactivator. Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNF14. The function of RNF14 has been established by previous studies. The RING finger motif is a unique

zinc–chelating domain involved in mediating protein–DNA and protein–protein interactions. Using the sequence of the partial cDNA clone HFB30 isolated by Ueki et al.

(1998) to screen a human fetal brain cDNA library, Ueki et al. (1999) cloned the full–length cDNA, which encoded a novel ring finger protein, RNF14. The deduced 474–amino acid protein has a calculated molecular mass of approximately 53 kD. RT–PCR analysis revealed ubiquitous expression of RNF14 in a wide variety of human tissues.

Kang et al. (1999) independently cloned RNF14, which they called ARA54 (androgen receptor–associated protein–54), by a yeast 2–hybrid screen of a prostate cDNA library. Northern blot analysis detected a major 3–kb transcript, with highest expression in testis, followed by thymus, spleen, colon, prostate, and uterus. Low expression was detected in small intestine and blood leukocytes. The RNF14 transcript was also strongly detected in 2 other prostate cell lines. A second transcript of 2 kb was detected in testis only. Kang et al. (1999) demonstrated that RNF14 can function as a coactivator for androgen–dependent transcription on both wildtype and mutant androgen receptor (OMIM Ref. No. 313700). They also showed that in the presence of a certain amount of

17-beta-estradiol or hydroxyflutamide, the transcriptional activity of a specific AR mutant was significantly enhanced, whereas that of wildtype and another AR mutant was not. The authors suggested that both RNF14 and the positions of the AR mutation might contribute to the specificity of AR-mediated transactivation. Ueki et al. (1999) determined that the RNF14 gene contains 9 exons and spans approximately 20 kb of genomic DNA. By somatic cell hybrid and radiation hybrid analyses, Ueki et al. (1999) mapped the RNF14 gene to chromosome 5q23.3-q31.1.

[31920] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31921] Ueki, N.; Seki, N.; Yano, K.; Masuho, Y.; Saito, T.; Muramatsu, M. : Isolation and characterization of a novel human gene (HFB30) which encodes a protein with a RING finger motif. *Biochim. Biophys. Acta* 232-236, 1999. ; and

[31922] Kang, H.-Y.; Yeh, S.; Fujimoto, N.; Chang, C. : Cloning and characterization of human prostate coactivator ARA54, a novel protein that associates with the androgen receptor. *J. Biol. Chem.*

[31923] Further studies establishing the function and utilities of



RNF14 are found in John Hopkins OMIM database record ID 605675, and in cited publications numbered 8810–967 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Family 22 (organic cation transporter), Member 5 (SLC22A5, Accession NM\_003060) is another VGAM827 host target gene. SLC22A5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC22A5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC22A5 BINDING SITE, designated SEQ ID:9029, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31924] Another function of VGAM827 is therefore inhibition of Solute Carrier Family 22 (organic cation transporter), Member 5 (SLC22A5, Accession NM\_003060). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC22A5. Syntaxin 7 (STX7, Accession NM\_003569) is another VGAM827 host target gene. STX7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by STX7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STX7 BINDING SITE, designated SEQ ID:9625, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31925] Another function of VGAM827 is therefore inhibition of Syntaxin 7 (STX7, Accession NM\_003569). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STX7. Surfeit 6 (SURF6, Accession NM\_006753) is another VGAM827 host target gene. SURF6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SURF6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SURF6 BINDING SITE, designated SEQ ID:13610, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31926] Another function of VGAM827 is therefore inhibition of Surfeit 6 (SURF6, Accession NM\_006753). Accordingly,

utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SURF6. Cdc42 Guanine Nucleotide Exchange Factor (GEF) 9 (ARHGEF9, Accession NM\_015185) is another VGAM827 host target gene. ARHGEF9 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ARHGEF9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGEF9 BINDING SITE, designated SEQ ID:17539, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31927] Another function of VGAM827 is therefore inhibition of Cdc42 Guanine Nucleotide Exchange Factor (GEF) 9 (ARHGEF9, Accession NM\_015185). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGEF9. Dedicator of Cyto-kinesis 3 (DOCK3, Accession XM\_039259) is another VGAM827 host target gene. DOCK3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DOCK3, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DOCK3 BINDING SITE, designated SEQ ID:33042, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31928] Another function of VGAM827 is therefore inhibition of Dedicator of Cyto-kinesis 3 (DOCK3, Accession XM\_039259). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DOCK3. FLJ14153 (Accession NM\_022736) is another VGAM827 host target gene. FLJ14153 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14153, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14153 BINDING SITE, designated SEQ ID:22942, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31929] Another function of VGAM827 is therefore inhibition of FLJ14153 (Accession NM\_022736). Accordingly, utilities of

VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14153. FLJ22127 (Accession NM\_022775) is another VGAM827 host target gene. FLJ22127 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22127, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22127 BINDING SITE, designated SEQ ID:23044, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31930] Another function of VGAM827 is therefore inhibition of FLJ22127 (Accession NM\_022775). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22127. KIAA0276 (Accession XM\_048199) is another VGAM827 host target gene. KIAA0276 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0276 BINDING SITE,

designated SEQ ID:35140, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31931] Another function of VGAM827 is therefore inhibition of KIAA0276 (Accession XM\_048199). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0276. KIAA0367 (Accession XM\_041018) is another VGAM827 host target gene. KIAA0367 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0367, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0367 BINDING SITE, designated SEQ ID:33427, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31932] Another function of VGAM827 is therefore inhibition of KIAA0367 (Accession XM\_041018). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0367. KIAA0494 (Accession NM\_014774) is another VGAM827 host target gene. KIAA0494 BINDING SITE is

HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0494, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0494 BINDING SITE, designated SEQ ID:16592, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31933] Another function of VGAM827 is therefore inhibition of KIAA0494 (Accession NM\_014774). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0494. KIAA1000 (Accession XM\_036988) is another VGAM827 host target gene. KIAA1000 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1000, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1000 BINDING SITE, designated SEQ ID:32536, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31934] Another function of VGAM827 is therefore inhibition of

KIAA1000 (Accession XM\_036988). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1000. KIAA1155 (Accession XM\_030864) is another VGAM827 host target gene. KIAA1155 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1155 BINDING SITE, designated SEQ ID:31203, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31935] Another function of VGAM827 is therefore inhibition of KIAA1155 (Accession XM\_030864). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1155. KIAA1437 (Accession XM\_026998) is another VGAM827 host target gene. KIAA1437 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1437, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the



complementarity of the nucleotide sequences of KIAA1437 BINDING SITE, designated SEQ ID:30386, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31936] Another function of VGAM827 is therefore inhibition of KIAA1437 (Accession XM\_026998). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1437. KIAA1884 (Accession XM\_055539) is another VGAM827 host target gene. KIAA1884 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1884, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1884 BINDING SITE, designated SEQ ID:36299, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31937] Another function of VGAM827 is therefore inhibition of KIAA1884 (Accession XM\_055539). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1884. NX-17 (Accession NM\_020665) is another

VGAM827 host target gene. NX-17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NX-17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NX-17 BINDING SITE, designated SEQ ID:21836, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31938] Another function of VGAM827 is therefore inhibition of NX-17 (Accession NM\_020665). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NX-17. Platelet-activating Factor Acetylhydrolase 2, 40kDa (PAFAH2, Accession NM\_000437) is another VGAM827 host target gene. PAFAH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAFAH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAFAH2 BINDING SITE, designated SEQ ID:6022, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3538.

[31939] Another function of VGAM827 is therefore inhibition of Platelet-activating Factor Acetylhydrolase 2, 40kDa (PAFAH2, Accession NM\_000437). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAFAH2. Placenta-specific 3 (PLAC3, Accession XM\_045115) is another VGAM827 host target gene. PLAC3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PLAC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLAC3 BINDING SITE, designated SEQ ID:34369, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31940] Another function of VGAM827 is therefore inhibition of Placenta-specific 3 (PLAC3, Accession XM\_045115). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLAC3. PRO2405 (Accession NM\_018627) is another VGAM827 host target gene. PRO2405 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by PRO2405, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2405 BINDING SITE, designated SEQ ID:20700, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31941] Another function of VGAM827 is therefore inhibition of PRO2405 (Accession NM\_018627). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2405. Roundabout, Axon Guidance Receptor, Homolog 2 (Drosophila) (ROBO2, Accession XM\_031246) is another VGAM827 host target gene. ROBO2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ROBO2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ROBO2 BINDING SITE, designated SEQ ID:31318, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31942] Another function of VGAM827 is therefore inhibition of

Roundabout, Axon Guidance Receptor, Homolog 2 (Drosophila) (ROBO2, Accession XM\_031246). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ROBO2. Sema Domain, Seven Thrombospondin Repeats (type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM\_003966) is another VGAM827 host target gene. SEMA5A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEMA5A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA5A BINDING SITE, designated SEQ ID:10107, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31943] Another function of VGAM827 is therefore inhibition of Sema Domain, Seven Thrombospondin Repeats (type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM\_003966). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with SEMA5A. LOC133688 (Accession XM\_059665) is another VGAM827 host target gene. LOC133688 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133688, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133688 BINDING SITE, designated SEQ ID:37051, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31944] Another function of VGAM827 is therefore inhibition of LOC133688 (Accession XM\_059665). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133688. LOC145815 (Accession XM\_096874) is another VGAM827 host target gene. LOC145815 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145815, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145815 BINDING SITE, designated SEQ ID:40608, to

the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31945] Another function of VGAM827 is therefore inhibition of LOC145815 (Accession XM\_096874). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145815. LOC153338 (Accession XM\_098361) is another VGAM827 host target gene. LOC153338 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153338, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153338 BINDING SITE, designated SEQ ID:41612, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31946] Another function of VGAM827 is therefore inhibition of LOC153338 (Accession XM\_098361). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153338. LOC155032 (Accession XM\_098647) is another VGAM827 host target gene. LOC155032 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC155032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155032 BINDING SITE, designated SEQ ID:41749, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31947] Another function of VGAM827 is therefore inhibition of LOC155032 (Accession XM\_098647). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155032. LOC155376 (Accession XM\_088240) is another VGAM827 host target gene. LOC155376 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC155376, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155376 BINDING SITE, designated SEQ ID:39564, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31948] Another function of VGAM827 is therefore inhibition of LOC155376 (Accession XM\_088240). Accordingly, utilities



of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155376. LOC158046 (Accession NM\_145283) is another VGAM827 host target gene. LOC158046 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC158046, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158046 BINDING SITE, designated SEQ ID:29801, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31949] Another function of VGAM827 is therefore inhibition of LOC158046 (Accession NM\_145283). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158046. LOC196527 (Accession XM\_113743) is another VGAM827 host target gene. LOC196527 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC196527, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC196527 BINDING SITE, designated SEQ ID:42403, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31950] Another function of VGAM827 is therefore inhibition of LOC196527 (Accession XM\_113743). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196527. LOC245728 (Accession XM\_165922) is another VGAM827 host target gene. LOC245728 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC245728, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC245728 BINDING SITE, designated SEQ ID:43803, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31951] Another function of VGAM827 is therefore inhibition of LOC245728 (Accession XM\_165922). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC245728. LOC253532 (Accession XM\_171152) is another VGAM827 host target gene. LOC253532 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC253532, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253532 BINDING SITE, designated SEQ ID:45950, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31952] Another function of VGAM827 is therefore inhibition of LOC253532 (Accession XM\_171152). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253532. LOC253613 (Accession XM\_171225) is another VGAM827 host target gene. LOC253613 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC253613, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253613 BINDING SITE, designated SEQ ID:46014, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31953] Another function of VGAM827 is therefore inhibition of

LOC253613 (Accession XM\_171225). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253613. LOC254337 (Accession XM\_172034) is another VGAM827 host target gene. LOC254337 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254337, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254337 BINDING SITE, designated SEQ ID:46066, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31954] Another function of VGAM827 is therefore inhibition of LOC254337 (Accession XM\_172034). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254337. LOC254875 (Accession XM\_171170) is another VGAM827 host target gene. LOC254875 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254875, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC254875 BINDING SITE, designated SEQ ID:45954, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31955] Another function of VGAM827 is therefore inhibition of LOC254875 (Accession XM\_171170). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254875. LOC51141 (Accession XM\_043953) is another VGAM827 host target gene. LOC51141 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51141, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51141 BINDING SITE, designated SEQ ID:34052, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31956] Another function of VGAM827 is therefore inhibition of LOC51141 (Accession XM\_043953). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51141. LOC90321 (Accession XM\_030896) is another

VGAM827 host target gene. LOC90321 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90321, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90321 BINDING SITE, designated SEQ ID:31213, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31957] Another function of VGAM827 is therefore inhibition of LOC90321 (Accession XM\_030896). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90321. LOC93349 (Accession NM\_138402) is another VGAM827 host target gene. LOC93349 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC93349, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93349 BINDING SITE, designated SEQ ID:28770, to the nucleotide sequence of VGAM827 RNA, herein designated VGAM RNA, also designated SEQ ID:3538.

[31958] Another function of VGAM827 is therefore inhibition of LOC93349 (Accession NM\_138402). Accordingly, utilities of VGAM827 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93349. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 828 (VGAM828) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[31959] VGAM828 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM828 was detected is described hereinabove with reference to Figs. 1–8.

[31960] VGAM828 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM828 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[31961] VGAM828 gene encodes a VGAM828 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM828

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM828 precursor RNA is designated SEQ ID:814, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:814 is located at position 13516 relative to the genome of African Swine Fever Virus.

[31962] VGAM828 precursor RNA folds onto itself, forming VGAM828 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[31963] An enzyme complex designated DICER COMPLEX, `dices` the VGAM828 folded precursor RNA into VGAM828 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other



necessary proteins. A probable (over 75%) nucleotide sequence of VGAM828 RNA is designated SEQ ID:3539, and is provided hereinbelow with reference to the sequence listing part.

[31964] VGAM828 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM828 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM828 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[31965] VGAM828 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM828 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM828 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM828 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM828 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[31966] The complementary binding of VGAM828 RNA, herein designated VGAM RNA, to host target binding sites on VGAM828 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM828 host target RNA into VGAM828 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[31967] It is appreciated that VGAM828 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM828 host target genes. The mRNA of each one of this plurality of VGAM828 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM828 RNA, herein designated VGAM RNA, and which when bound by VGAM828 RNA causes inhibition of translation of respective one or more VGAM828 host target proteins.

[31968] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM828 gene, herein designated VGAM GENE, on one or more VGAM828 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[31969] It is yet further appreciated that a function of VGAM828 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus. Specific functions, and accordingly utilities, of VGAM828 correlate with, and may be deduced from, the identity of the host target genes which VGAM828 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[31970] Nucleotide sequences of the VGAM828 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM828 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM828 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM828 are further described hereinbelow with reference to Table 1.

[31971] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM828 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM828 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[31972] As mentioned hereinabove with reference to Fig. 1, a function of VGAM828 gene, herein designated VGAM is inhibition of expression of VGAM828 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM828 correlate with, and may be deduced from, the identity of the target genes which VGAM828 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[31973] D12S2489E (Accession NM\_007360) is a VGAM828 host target gene. D12S2489E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by D12S2489E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of D12S2489E BINDING SITE, designated SEQ ID:14293, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31974] A function of VGAM828 is therefore inhibition of D12S2489E (Accession NM\_007360), a gene which interacts in the inhibition and activation of NK cells. Accordingly, utilities of VGAM828 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with D12S2489E. The function of D12S2489E and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM156. Nuclear Receptor Coactivator 6 (NCOA6, Accession NM\_014071) is another VGAM828 host target gene. NCOA6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NCOA6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA6 BINDING SITE, designated SEQ ID:15291, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31975] Another function of VGAM828 is therefore inhibition of Nuclear Receptor Coactivator 6 (NCOA6, Accession NM\_014071), a gene which activates gene transcription through ligand-dependent association with coactivators. Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA6. The function of NCOA6 and its association with various diseases and clinical conditions,

has been established by previous studies, as described hereinabove with reference to VGAM25. Phosphoribosyl Pyrophosphate Synthetase 2 (PRPS2, Accession NM\_002765) is another VGAM828 host target gene. PRPS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRPS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRPS2 BINDING SITE, designated SEQ ID:8658, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31976] Another function of VGAM828 is therefore inhibition of Phosphoribosyl Pyrophosphate Synthetase 2 (PRPS2, Accession NM\_002765), a gene which generates the PRPP needed for initiation of purine biosynthesis. Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRPS2. The function of PRPS2 has been established by previous studies. Five-phosphoribosyl 1-pyrophosphate (OMIM Ref. No. PPRibP), an essential substrate and a critical regulator in the purine, pyrimidine, and pyridine nucleotide production pathways, is synthe-

sized from MgATP and ribose 5-phosphate by the enzyme PPRibP synthetase (EC 2.7.6.1). By cDNA cloning, Taira et al. (1987) found 2 distinct PPRibP synthetase subunits, PRS I (PRPS1; 311850) and PRS II. By screening a testis library with a rat PRS II cDNA, Iizasa et al. (1989) isolated cDNAs encoding human PRS II. The predicted 318-amino acid protein shares 99% identity with rat PRS II. Northern blot analysis revealed that PRS II is expressed as a 2.7-kb mRNA in testis. By using a rat cDNA probe for PRPS1 and a human cDNA probe for PRPS2, Taira et al. (1989) showed in DNA from somatic cell hybrids and in spot-blot hybridization of flow-sorted chromosomes that whereas PRPS1 is on Xq21-qter, PRPS2 is on Xpter-q21. Furthermore, 2 PRPS1-related genes were identified on chromosomes 7 and 9. By a combination of in situ hybridization and study of human/rodent somatic cell hybrids, Becker et al. (1990) assigned the PRPS2 locus to Xp22.3-p22.2. Despite the striking homology in the cDNA sequence and deduced amino acid sequence, PRPS1 and PRPS2 are encoded by genes on opposite arms of the X chromosome. Wang et al. (1992) demonstrated that the PRPS2 gene is inactivated with lyonization but that it lies between 2 genes that escape inactivation, STS (OMIM Ref. No.



308100) distally and ZFX (OMIM Ref. No. 314980) proximally. The PRPS1 gene also undergoes X inactivation. Wang et al. (1992) commented that it was not known which of the 2 PRPS loci is altered in patients with inherited PRPS superactivity. The ZFX gene, which escapes X-inactivation, is bracketed proximally by the POLA gene (OMIM Ref. No. 312040) which, like PRPS2, undergoes inactivation. The A1S9T (OMIM Ref. No. 314370) locus in the proximal short arm and the RPS4X gene (OMIM Ref. No. 312760) in the proximal long arm are other loci that escape inactivation and are interspersed among genes that do undergo X-inactivation. Furthermore, the XIST gene (OMIM Ref. No. 314670), located at Xq13, is transcribed only from the inactive X chromosome

[31977] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[31978] Taira, M.; Kudoh, J.; Minoshima, S.; Iizasa, T.; Shimada, H.; Shimizu, Y.; Tatibana, M.; Shimizu, N. : Localization of human phosphoribosylpyrophosphate synthetase subunit I and II genes (PRPS1 and PRPS2) to different regions of the X chromosome and assignment of two PRPS1-related genes to autosomes. *Somat. Cell Molec. Genet.* 15: 29-37,

1989. ; and

[31979] Wang, J. C.; Passage, M. B.; Ellison, J.; Becker, M. A.; Yen, P. H.; Shapiro, L. J.; Mohandas, T. K. : Physical mapping of loci in the distal half of the short arm of the human X chromos.

[31980] Further studies establishing the function and utilities of PRPS2 are found in John Hopkins OMIM database record ID 311860, and in cited publications numbered 8345–1234 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Sex Comb On Midleg-like 1 (Drosophila) (SCML1, Accession NM\_006746) is another VGAM828 host target gene. SCML1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SCML1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCML1 BINDING SITE, designated SEQ ID:13594, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31981] Another function of VGAM828 is therefore inhibition of Sex Comb On Midleg-like 1 (Drosophila) (SCML1, Accession NM\_006746). Accordingly, utilities of VGAM828 in–

clude diagnosis, prevention and treatment of diseases and clinical conditions associated with SCML1. Sel-1 Suppressor of Lin-12-like (C. elegans) (SEL1L, Accession NM\_005065) is another VGAM828 host target gene. SEL1L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEL1L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEL1L BINDING SITE, designated SEQ ID:11504, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31982] Another function of VGAM828 is therefore inhibition of Sel-1 Suppressor of Lin-12-like (C. elegans) (SEL1L, Accession NM\_005065), a gene which may play a role in notch signaling (by similarity). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEL1L. The function of SEL1L and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM245. Single-minded Homolog 1 (Drosophila) (SIM1, Accession NM\_005068) is another VGAM828 host

target gene. SIM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIM1 BINDING SITE, designated SEQ ID:11514, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31983] Another function of VGAM828 is therefore inhibition of Single-minded Homolog 1 (Drosophila) (SIM1, Accession NM\_005068), a gene which may have pleiotropic effects during embryogenesis and in the adult. Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIM1. The function of SIM1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM665.Sparc/osteonectin, Cwcv and Kazal-like Domains Proteoglycan (testican) (SPOCK, Accession XM\_031696) is another VGAM828 host target gene. SPOCK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

SPOCK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPOCK BINDING SITE, designated SEQ ID:31459, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31984] Another function of VGAM828 is therefore inhibition of Sparc/osteonectin, Cwcv and Kazal-like Domains Proteoglycan (testican) (SPOCK, Accession XM\_031696). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPOCK. B1 (Accession NM\_014451) is another VGAM828 host target gene. B1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B1 BINDING SITE, designated SEQ ID:15801, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31985] Another function of VGAM828 is therefore inhibition of B1

(Accession NM\_014451). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B1.

FLJ14281 (Accession NM\_024920) is another VGAM828 host target gene. FLJ14281 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14281, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14281 BINDING SITE, designated SEQ ID:24453, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31986] Another function of VGAM828 is therefore inhibition of FLJ14281 (Accession NM\_024920). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14281. HSPC019 (Accession NM\_014028) is another VGAM828 host target gene. HSPC019 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPC019, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of HSPC019 BINDING SITE, designated SEQ ID:15254, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31987] Another function of VGAM828 is therefore inhibition of HSPC019 (Accession NM\_014028). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC019. KIAA0296 (Accession NM\_014699) is another VGAM828 host target gene. KIAA0296 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0296, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0296 BINDING SITE, designated SEQ ID:16224, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31988] Another function of VGAM828 is therefore inhibition of KIAA0296 (Accession NM\_014699). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0296. KIAA0453 (Accession XM\_044546) is another

VGAM828 host target gene. KIAA0453 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0453, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0453 BINDING SITE, designated SEQ ID:34231, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31989] Another function of VGAM828 is therefore inhibition of KIAA0453 (Accession XM\_044546). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0453. KR18 (Accession NM\_033288) is another VGAM828 host target gene. KR18 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KR18, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KR18 BINDING SITE, designated SEQ ID:27120, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.



[31990] Another function of VGAM828 is therefore inhibition of KR18 (Accession NM\_033288). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KR18. LAT1-3TM (Accession NM\_031211) is another VGAM828 host target gene. LAT1-3TM BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LAT1-3TM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LAT1-3TM BINDING SITE, designated SEQ ID:25253, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31991] Another function of VGAM828 is therefore inhibition of LAT1-3TM (Accession NM\_031211). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LAT1-3TM. MEGF10 (Accession NM\_032446) is another VGAM828 host target gene. MEGF10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MEGF10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEGF10 BINDING SITE, designated SEQ ID:26214, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31992] Another function of VGAM828 is therefore inhibition of MEGF10 (Accession NM\_032446). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEGF10. MGC2488 (Accession NM\_024039) is another VGAM828 host target gene. MGC2488 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2488, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2488 BINDING SITE, designated SEQ ID:23474, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31993] Another function of VGAM828 is therefore inhibition of MGC2488 (Accession NM\_024039). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

MGC2488. Stromal Interaction Molecule 2 (STIM2, Accession NM\_020860) is another VGAM828 host target gene. STIM2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by STIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STIM2 BINDING SITE, designated SEQ ID:21917, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31994] Another function of VGAM828 is therefore inhibition of Stromal Interaction Molecule 2 (STIM2, Accession NM\_020860). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STIM2. LOC120103 (Accession XM\_058449) is another VGAM828 host target gene. LOC120103 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC120103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120103 BINDING SITE, desig-

nated SEQ ID:36619, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31995] Another function of VGAM828 is therefore inhibition of LOC120103 (Accession XM\_058449). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120103. LOC138639 (Accession XM\_059988) is another VGAM828 host target gene. LOC138639 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC138639, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC138639 BINDING SITE, designated SEQ ID:37140, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31996] Another function of VGAM828 is therefore inhibition of LOC138639 (Accession XM\_059988). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC138639. LOC145945 (Accession XM\_096908) is another VGAM828 host target gene. LOC145945 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145945, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145945 BINDING SITE, designated SEQ ID:40635, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31997] Another function of VGAM828 is therefore inhibition of LOC145945 (Accession XM\_096908). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145945. LOC197423 (Accession XM\_085436) is another VGAM828 host target gene. LOC197423 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC197423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197423 BINDING SITE, designated SEQ ID:38144, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31998] Another function of VGAM828 is therefore inhibition of

LOC197423 (Accession XM\_085436). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197423. LOC220672 (Accession XM\_017177) is another VGAM828 host target gene. LOC220672 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220672, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220672 BINDING SITE, designated SEQ ID:30310, to the nucleotide sequence of VGAM828 RNA, herein designated VGAM RNA, also designated SEQ ID:3539.

[31999] Another function of VGAM828 is therefore inhibition of LOC220672 (Accession XM\_017177). Accordingly, utilities of VGAM828 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220672. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 829 (VGAM829) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[32000] VGAM829 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM829 was detected is described hereinabove with reference to Figs. 1–8.

[32001] VGAM829 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM829 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32002] VGAM829 gene encodes a VGAM829 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM829 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM829 precursor RNA is designated SEQ ID:815, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:815 is located at position 13995 relative to the genome of African Swine Fever Virus.

[32003] VGAM829 precursor RNA folds onto itself, forming VGAM829 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[32004] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM829 folded precursor RNA into VGAM829 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM829 RNA is designated SEQ ID:3540, and  
is provided hereinbelow with reference to the sequence  
listing part.

[32005] VGAM829 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM829 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM829 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region



and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32006] VGAM829 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM829 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM829 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM829 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM829 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[32007] The complementary binding of VGAM829 RNA, herein designated VGAM RNA, to host target binding sites on VGAM829 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM829 host target RNA into VGAM829 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32008] It is appreciated that VGAM829 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM829 host target genes. The mRNA of each one of this plurality of VGAM829 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM829 RNA, herein designated VGAM RNA, and which when bound by VGAM829 RNA causes inhibition of translation of respective one or more VGAM829 host target proteins.

[32009] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM829 gene, herein designated VGAM GENE, on one or

more VGAM829 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32010] It is yet further appreciated that a function of VGAM829 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus. Specific functions, and accordingly utilities, of VGAM829 correlate with, and may be deduced from, the identity of the host target genes which VGAM829 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [32011] Nucleotide sequences of the VGAM829 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM829 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM829 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM829 are further described hereinbelow with reference to Table 1.
- [32012] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM829 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM829 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [32013] As mentioned hereinabove with reference to Fig. 1, a function of VGAM829 gene, herein designated VGAM is inhibition of expression of VGAM829 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM829 correlate with, and may be deduced from, the identity of the target genes which VGAM829 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [32014] Transcription Factor 12 (HTF4, helix-loop-helix transcrip-

tion factors 4) (TCF12, Accession NM\_003205) is a VGAM829 host target gene. TCF12 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TCF12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCF12 BINDING SITE, designated SEQ ID:9201, to the nucleotide sequence of VGAM829 RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32015] A function of VGAM829 is therefore inhibition of Transcription Factor 12 (HTF4, helix-loop-helix transcription factors 4) (TCF12, Accession NM\_003205), a gene which may play important roles during development of the nervous system as well as in other organ systems. Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCF12. The function of TCF12 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM308.UDP-GlcNAc:betaGal Beta-1,3-N-acetylglucosaminyltransferase 7 (B3GNT7, Accession XM\_048735) is another VGAM829 host target

gene. B3GNT7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by B3GNT7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B3GNT7 BINDING SITE, designated SEQ ID:35239, to the nucleotide sequence of VGAM829 RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32016] Another function of VGAM829 is therefore inhibition of UDP-GlcNAc:betaGal Beta-1,3-N-acetylglucosaminyltransferase 7 (B3GNT7, Accession XM\_048735). Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B3GNT7. KIAA1344 (Accession XM\_051699) is another VGAM829 host target gene. KIAA1344 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1344, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1344 BINDING SITE, designated SEQ ID:35872, to the nucleotide sequence of VGAM829

RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32017] Another function of VGAM829 is therefore inhibition of KIAA1344 (Accession XM\_051699). Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1344. KIAA1894 (Accession XM\_058025) is another VGAM829 host target gene. KIAA1894 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1894 BINDING SITE, designated SEQ ID:36562, to the nucleotide sequence of VGAM829 RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32018] Another function of VGAM829 is therefore inhibition of KIAA1894 (Accession XM\_058025). Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1894. PIP3-E (Accession XM\_039749) is another VGAM829 host target gene. PIP3-E BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by PIP3-E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIP3-E BINDING SITE, designated SEQ ID:33175, to the nucleotide sequence of VGAM829 RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32019] Another function of VGAM829 is therefore inhibition of PIP3-E (Accession XM\_039749). Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP3-E. Ubiquitin-conjugating Enzyme E2 Variant 2 (UBE2V2, Accession NM\_003350) is another VGAM829 host target gene. UBE2V2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2V2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2V2 BINDING SITE, designated SEQ ID:9377, to the nucleotide sequence of VGAM829 RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32020] Another function of VGAM829 is therefore inhibition of



Ubiquitin-conjugating Enzyme E2 Variant 2 (UBE2V2, Accession NM\_003350). Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2V2.

LOC253143 (Accession XM\_173062) is another VGAM829 host target gene. LOC253143 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC253143, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253143 BINDING SITE, designated SEQ ID:46316, to the nucleotide sequence of VGAM829 RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32021] Another function of VGAM829 is therefore inhibition of LOC253143 (Accession XM\_173062). Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253143. LOC254170 (Accession XM\_170746) is another VGAM829 host target gene. LOC254170 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254170, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254170 BINDING SITE, designated SEQ ID:45505, to the nucleotide sequence of VGAM829 RNA, herein designated VGAM RNA, also designated SEQ ID:3540.

[32022] Another function of VGAM829 is therefore inhibition of LOC254170 (Accession XM\_170746). Accordingly, utilities of VGAM829 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254170. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 830 (VGAM830) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32023] VGAM830 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM830 was detected is described hereinabove with reference to Figs. 1–8.

[32024] VGAM830 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM830 host target gene, herein designated

VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32025] VGAM830 gene encodes a VGAM830 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM830 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM830 precursor RNA is designated SEQ ID:816, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:816 is located at position 11737 relative to the genome of African Swine Fever Virus.

[32026] VGAM830 precursor RNA folds onto itself, forming VGAM830 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32027] An enzyme complex designated DICER COMPLEX, `dices` the VGAM830 folded precursor RNA into VGAM830 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 54%) nucleotide sequence of VGAM830 RNA is designated SEQ ID:3541, and is provided hereinbelow with reference to the sequence listing part.

[32028] VGAM830 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM830 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM830 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32029] VGAM830 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM830 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM830 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM830 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM830 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32030] The complementary binding of VGAM830 RNA, herein designated VGAM RNA, to host target binding sites on VGAM830 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM830 host target RNA into VGAM830 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[32031] It is appreciated that VGAM830 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM830 host target genes. The mRNA of each one of this plurality of VGAM830 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM830 RNA, herein designated VGAM RNA, and which when bound by VGAM830 RNA causes inhibition of translation of respective one or more VGAM830 host target proteins.

[32032] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM830 gene, herein designated VGAM GENE, on one or more VGAM830 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32033] It is yet further appreciated that a function of VGAM830 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus. Specific functions, and accordingly utilities, of VGAM830 correlate with, and may be deduced from, the identity of the host target genes which VGAM830 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32034] Nucleotide sequences of the VGAM830 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM830 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM830 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM830 are further described hereinbelow with reference to Table 1.

[32035] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM830 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM830 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32036] As mentioned hereinabove with reference to Fig. 1, a function of VGAM830 gene, herein designated VGAM is inhibition of expression of VGAM830 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM830 correlate with, and may be deduced from, the identity of the target genes which VGAM830 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32037] Moesin (MSN, Accession XM\_013042) is a VGAM830 host target gene. MSN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSN BINDING SITE, designated SEQ ID:30225, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ



ID:3541.

[32038] A function of VGAM830 is therefore inhibition of Moesin (MSN, Accession XM\_013042), a gene which may have a role linking the cytoskeleton to the plasma membrane. Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSN. The function of MSN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM248. Pleiomorphic Adenoma Gene 1 (PLAG1, Accession NM\_002655) is another VGAM830 host target gene. PLAG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PLAG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLAG1 BINDING SITE, designated SEQ ID:8523, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32039] Another function of VGAM830 is therefore inhibition of Pleiomorphic Adenoma Gene 1 (PLAG1, Accession NM\_002655), a gene which contains a zinc finger domain.

Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLAG1. The function of PLAG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM29. Ubiquitously Transcribed Tetratricopeptide Repeat Gene, Y Chromosome (UTY, Accession NM\_007125) is another VGAM830 host target gene. UTY BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UTY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UTY BINDING SITE, designated SEQ ID:13982, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32040] Another function of VGAM830 is therefore inhibition of Ubiquitously Transcribed Tetratricopeptide Repeat Gene, Y Chromosome (UTY, Accession NM\_007125), a gene which is an ubiquitous tetratricopeptide repeat protein with unknown function. Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with UTY. The function of UTY and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM497. ABLIM (Accession NM\_002313) is another VGAM830 host target gene. ABLIM BINDING SITE1 and ABLIM BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABLIM, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABLIM BINDING SITE1 and ABLIM BINDING SITE2, designated SEQ ID:8113 and SEQ ID:13546 respectively, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32041] Another function of VGAM830 is therefore inhibition of ABLIM (Accession NM\_002313). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABLIM. KIAA0650 (Accession XM\_113962) is another VGAM830 host target gene. KIAA0650 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0650, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0650 BINDING SITE, designated SEQ ID:42570, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32042] Another function of VGAM830 is therefore inhibition of KIAA0650 (Accession XM\_113962). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0650. KIAA1560 (Accession XM\_034422) is another VGAM830 host target gene. KIAA1560 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1560, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1560 BINDING SITE, designated SEQ ID:32103, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32043] Another function of VGAM830 is therefore inhibition of KIAA1560 (Accession XM\_034422). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1560. TUSP (Accession NM\_020245) is another VGAM830 host target gene. TUSP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TUSP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TUSP BINDING SITE, designated SEQ ID:21529, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32044] Another function of VGAM830 is therefore inhibition of TUSP (Accession NM\_020245). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TUSP. LOC126731 (Accession NM\_145257) is another VGAM830 host target gene. LOC126731 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC126731, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126731 BINDING SITE, designated SEQ ID:29772, to the nucleotide se-

quence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32045] Another function of VGAM830 is therefore inhibition of LOC126731 (Accession NM\_145257). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126731. LOC129831 (Accession XM\_059376) is another VGAM830 host target gene. LOC129831 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC129831, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC129831 BINDING SITE, designated SEQ ID:36979, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32046] Another function of VGAM830 is therefore inhibition of LOC129831 (Accession XM\_059376). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129831. LOC157858 (Accession XM\_098833) is another VGAM830 host target gene. LOC157858 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC157858, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157858 BINDING SITE, designated SEQ ID:41868, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32047] Another function of VGAM830 is therefore inhibition of LOC157858 (Accession XM\_098833). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157858. LOC199718 (Accession XM\_113998) is another VGAM830 host target gene. LOC199718 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC199718, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199718 BINDING SITE, designated SEQ ID:42606, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32048] Another function of VGAM830 is therefore inhibition of LOC199718 (Accession XM\_113998). Accordingly, utilities

of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199718. LOC221288 (Accession XM\_168058) is another VGAM830 host target gene. LOC221288 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221288, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221288 BINDING SITE, designated SEQ ID:44972, to the nucleotide sequence of VGAM830 RNA, herein designated VGAM RNA, also designated SEQ ID:3541.

[32049] Another function of VGAM830 is therefore inhibition of LOC221288 (Accession XM\_168058). Accordingly, utilities of VGAM830 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221288. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 831 (VGAM831) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.



[32050] VGAM831 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM831 was detected is described hereinabove with reference to Figs. 1–8.

[32051] VGAM831 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 6B. VGAM831 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32052] VGAM831 gene encodes a VGAM831 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM831 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM831 precursor RNA is designated SEQ ID:817, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:817 is located at position 53746 relative to the genome of Human Herpesvirus 6B.

[32053] VGAM831 precursor RNA folds onto itself, forming VGAM831 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32054] An enzyme complex designated DICER COMPLEX, `dices` the VGAM831 folded precursor RNA into VGAM831 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 55%) nucleotide sequence of VGAM831 RNA is designated SEQ ID:3542, and is provided hereinbelow with reference to the sequence listing part.

[32055] VGAM831 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM831 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM831 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[32056] VGAM831 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM831 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM831 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM831 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM831 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32057] The complementary binding of VGAM831 RNA, herein designated VGAM RNA, to host target binding sites on VGAM831 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM831 host target RNA into VGAM831 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32058] It is appreciated that VGAM831 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM831 host target genes. The mRNA of each one of this plurality of VGAM831 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM831 RNA, herein designated VGAM RNA, and which when bound by VGAM831 RNA causes inhibition of translation of respective one or more VGAM831 host target proteins.

[32059] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM831 gene, herein designated VGAM GENE, on one or more VGAM831 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32060] It is yet further appreciated that a function of VGAM831 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM831 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 6B. Specific functions, and accordingly utilities, of VGAM831 correlate with, and may be deduced from, the identity of the host target genes which VGAM831 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32061] Nucleotide sequences of the VGAM831 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM831 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM831 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM831 are further  
described hereinbelow with reference to Table 1.

[32062] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM831 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM831 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[32063] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM831 gene, herein designated VGAM is  
inhibition of expression of VGAM831 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM831 correlate with, and may be deduced  
from, the identity of the target genes which VGAM831  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[32064] Deleted In Azoospermia (DAZ, Accession NM\_004081) is a  
VGAM831 host target gene. DAZ BINDING SITE is HOST

TARGET binding site found in the 3` untranslated region of mRNA encoded by DAZ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAZ BINDING SITE, designated SEQ ID:10285, to the nucleotide sequence of VGAM831 RNA, herein designated VGAM RNA, also designated SEQ ID:3542.

[32065] A function of VGAM831 is therefore inhibition of Deleted In Azoospermia (DAZ, Accession NM\_004081), a gene which may play a role in the germ-cell-specific patterns of RNA splicing and storage. Accordingly, utilities of VGAM831 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAZ. The function of DAZ and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM206.DKFZp434N074 (Accession XM\_031481) is another VGAM831 host target gene. DKFZp434N074 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZp434N074, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2

illustrates the complementarity of the nucleotide sequences of DKFZp434N074 BINDING SITE, designated SEQ ID:31390, to the nucleotide sequence of VGAM831 RNA, herein designated VGAM RNA, also designated SEQ ID:3542.

[32066] Another function of VGAM831 is therefore inhibition of DKFZp434N074 (Accession XM\_031481). Accordingly, utilities of VGAM831 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434N074. FLJ10140 (Accession NM\_018006) is another VGAM831 host target gene. FLJ10140 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10140, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10140 BINDING SITE, designated SEQ ID:19738, to the nucleotide sequence of VGAM831 RNA, herein designated VGAM RNA, also designated SEQ ID:3542.

[32067] Another function of VGAM831 is therefore inhibition of FLJ10140 (Accession NM\_018006). Accordingly, utilities of VGAM831 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10140.



LOC201780 (Accession XM\_114378) is another VGAM831 host target gene. LOC201780 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC201780, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201780 BINDING SITE, designated SEQ ID:42910, to the nucleotide sequence of VGAM831 RNA, herein designated VGAM RNA, also designated SEQ ID:3542.

[32068] Another function of VGAM831 is therefore inhibition of LOC201780 (Accession XM\_114378). Accordingly, utilities of VGAM831 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201780. LOC256160 (Accession XM\_171079) is another VGAM831 host target gene. LOC256160 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256160, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256160 BINDING SITE, designated SEQ ID:45886, to the nucleotide sequence of VGAM831 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3542.

[32069] Another function of VGAM831 is therefore inhibition of LOC256160 (Accession XM\_171079). Accordingly, utilities of VGAM831 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256160. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 832 (VGAM832) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32070] VGAM832 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM832 was detected is described hereinabove with reference to Figs. 1–8.

[32071] VGAM832 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 6B. VGAM832 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32072] VGAM832 gene encodes a VGAM832 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM832 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM832 precursor RNA is designated SEQ ID:818, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:818 is located at position 52788 relative to the genome of Human Herpesvirus 6B.

[32073] VGAM832 precursor RNA folds onto itself, forming VGAM832 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32074] An enzyme complex designated DICER COMPLEX, `dices` the VGAM832 folded precursor RNA into VGAM832 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM832 RNA is designated SEQ ID:3543, and is provided hereinbelow with reference to the sequence listing part.

[32075] VGAM832 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM832 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM832 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32076] VGAM832 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM832 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM832 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM832 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM832 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32077] The complementary binding of VGAM832 RNA, herein designated VGAM RNA, to host target binding sites on VGAM832 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM832 host target RNA into VGAM832 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32078] It is appreciated that VGAM832 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM832 host target genes. The mRNA of

each one of this plurality of VGAM832 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM832 RNA, herein designated VGAM RNA, and which when bound by VGAM832 RNA causes inhibition of translation of respective one or more VGAM832 host target proteins.

[32079] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM832 gene, herein designated VGAM GENE, on one or more VGAM832 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[32080] It is yet further appreciated that a function of VGAM832 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM832 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 6B. Specific functions, and accordingly utilities, of VGAM832 correlate with, and may be deduced from, the identity of the host target genes which VGAM832 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32081] Nucleotide sequences of the VGAM832 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM832 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM832 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM832 are further described hereinbelow with reference to Table 1.

[32082] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM832 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM832 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[32083] As mentioned hereinabove with reference to Fig. 1, a function of VGAM832 gene, herein designated VGAM is inhibition of expression of VGAM832 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM832 correlate with, and may be deduced from, the identity of the target genes which VGAM832 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32084] Selenoprotein N, 1 (SEPN1, Accession XM\_039033) is a VGAM832 host target gene. SEPN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEPN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEPN1 BINDING SITE, designated SEQ ID:32992, to the nucleotide sequence of VGAM832 RNA, herein designated VGAM RNA, also designated SEQ ID:3543.

[32085] A function of VGAM832 is therefore inhibition of Selenoprotein N, 1 (SEPN1, Accession XM\_039033). Accordingly, utilities of VGAM832 include diagnosis, prevention and



treatment of diseases and clinical conditions associated with SEPN1. KIAA1055 (Accession XM\_038509) is another VGAM832 host target gene. KIAA1055 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1055, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1055 BINDING SITE, designated SEQ ID:32852, to the nucleotide sequence of VGAM832 RNA, herein designated VGAM RNA, also designated SEQ ID:3543.

[32086] Another function of VGAM832 is therefore inhibition of KIAA1055 (Accession XM\_038509). Accordingly, utilities of VGAM832 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1055. KIAA1951 (Accession XM\_057401) is another VGAM832 host target gene. KIAA1951 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1951, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1951 BINDING SITE, designated SEQ ID:36513, to the

nucleotide sequence of VGAM832 RNA, herein designated VGAM RNA, also designated SEQ ID:3543.

[32087] Another function of VGAM832 is therefore inhibition of KIAA1951 (Accession XM\_057401). Accordingly, utilities of VGAM832 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1951. NYD-SP27 (Accession NM\_033123) is another VGAM832 host target gene. NYD-SP27 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by NYD-SP27, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP27 BINDING SITE, designated SEQ ID:26968, to the nucleotide sequence of VGAM832 RNA, herein designated VGAM RNA, also designated SEQ ID:3543.

[32088] Another function of VGAM832 is therefore inhibition of NYD-SP27 (Accession NM\_033123). Accordingly, utilities of VGAM832 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP27. LOC92223 (Accession XM\_043674) is another VGAM832 host target gene. LOC92223 BINDING SITE is HOST TARGET binding site found in the 5` untranslated

region of mRNA encoded by LOC92223, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92223 BINDING SITE, designated SEQ ID:33995, to the nucleotide sequence of VGAM832 RNA, herein designated VGAM RNA, also designated SEQ ID:3543.

[32089] Another function of VGAM832 is therefore inhibition of LOC92223 (Accession XM\_043674). Accordingly, utilities of VGAM832 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92223. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 833 (VGAM833) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32090] VGAM833 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM833 was detected is described hereinabove with reference to Figs. 1–8.

[32091] VGAM833 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Monkeypox Virus.

VGAM833 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32092] VGAM833 gene encodes a VGAM833 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM833 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM833 precursor RNA is designated SEQ ID:819, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:819 is located at position 185114 relative to the genome of Monkeypox Virus.

[32093] VGAM833 precursor RNA folds onto itself, forming VGAM833 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32094] An enzyme complex designated DICER COMPLEX, `dices` the VGAM833 folded precursor RNA into VGAM833 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 64%) nucleotide sequence of VGAM833 RNA is designated SEQ ID:3544, and is provided hereinbelow with reference to the sequence listing part.

[32095] VGAM833 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM833 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM833 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32096] VGAM833 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM833 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM833 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM833 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM833 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32097] The complementary binding of VGAM833 RNA, herein designated VGAM RNA, to host target binding sites on VGAM833 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM833 host tar-

get RNA into VGAM833 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32098] It is appreciated that VGAM833 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM833 host target genes. The mRNA of each one of this plurality of VGAM833 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM833 RNA, herein designated VGAM RNA, and which when bound by VGAM833 RNA causes inhibition of translation of respective one or more VGAM833 host target proteins.

[32099] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM833 gene, herein designated VGAM GENE, on one or more VGAM833 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32100] It is yet further appreciated that a function of VGAM833 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM833 correlate with, and may be deduced from, the identity of the host target genes which VGAM833 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32101] Nucleotide sequences of the VGAM833 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM833 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM833 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM833 are further



described hereinbelow with reference to Table 1.

[32102] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM833 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM833 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32103] As mentioned hereinabove with reference to Fig. 1, a function of VGAM833 gene, herein designated VGAM is inhibition of expression of VGAM833 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM833 correlate with, and may be deduced from, the identity of the target genes which VGAM833 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32104] Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 2 (CBFA2T2, Accession NM\_005093) is a VGAM833 host target gene. CBFA2T2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CBFA2T2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of CBFA2T2 BINDING SITE, designated SEQ ID:11546, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32105] A function of VGAM833 is therefore inhibition of Core-binding Factor, Runt Domain, Alpha Subunit 2; Translocated To, 2 (CBFA2T2, Accession NM\_005093), a gene which is a putative transcription factor. Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CBFA2T2. The function of CBFA2T2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152.T-cell Acute Lymphocytic Leukemia 1 (TAL1, Accession NM\_003189) is another VGAM833 host target gene. TAL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TAL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAL1 BINDING SITE, designated SEQ ID:9173, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3544.

[32106] Another function of VGAM833 is therefore inhibition of T-cell Acute Lymphocytic Leukemia 1 (TAL1, Accession NM\_003189), a gene which may help control cell growth and differentiation. Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAL1. The function of TAL1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM172.KIAA0798 (Accession NM\_014650) is another VGAM833 host target gene. KIAA0798 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0798, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0798 BINDING SITE, designated SEQ ID:16067, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32107] Another function of VGAM833 is therefore inhibition of KIAA0798 (Accession NM\_014650). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0798. KIAA1155 (Accession XM\_030864) is another VGAM833 host target gene. KIAA1155 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1155 BINDING SITE, designated SEQ ID:31198, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32108] Another function of VGAM833 is therefore inhibition of KIAA1155 (Accession XM\_030864). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1155. Myosin, Heavy Polypeptide 10, Non-muscle (MYH10, Accession XM\_044702) is another VGAM833 host target gene. MYH10 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MYH10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYH10 BINDING SITE, designated

SEQ ID:34265, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32109] Another function of VGAM833 is therefore inhibition of Myosin, Heavy Polypeptide 10, Non-muscle (MYH10, Accession XM\_044702). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYH10.

LOC154739 (Accession XM\_098602) is another VGAM833 host target gene. LOC154739 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154739, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154739 BINDING SITE, designated SEQ ID:41713, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32110] Another function of VGAM833 is therefore inhibition of LOC154739 (Accession XM\_098602). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154739. LOC203276 (Accession XM\_117523) is an-

other VGAM833 host target gene. LOC203276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203276 BINDING SITE, designated SEQ ID:43480, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32111] Another function of VGAM833 is therefore inhibition of LOC203276 (Accession XM\_117523). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203276. LOC203305 (Accession XM\_117529) is another VGAM833 host target gene. LOC203305 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203305, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203305 BINDING SITE, designated SEQ ID:43504, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32112] Another function of VGAM833 is therefore inhibition of LOC203305 (Accession XM\_117529). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203305. LOC254243 (Accession XM\_173233) is another VGAM833 host target gene. LOC254243 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254243, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254243 BINDING SITE, designated SEQ ID:46506, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32113] Another function of VGAM833 is therefore inhibition of LOC254243 (Accession XM\_173233). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254243. LOC51131 (Accession NM\_016119) is another VGAM833 host target gene. LOC51131 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51131, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51131 BINDING SITE, designated SEQ ID:18201, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32114] Another function of VGAM833 is therefore inhibition of LOC51131 (Accession NM\_016119). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51131. LOC90038 (Accession XM\_028305) is another VGAM833 host target gene. LOC90038 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90038 BINDING SITE, designated SEQ ID:30643, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32115] Another function of VGAM833 is therefore inhibition of LOC90038 (Accession XM\_028305). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC90038. LOC91115 (Accession XM\_036218) is another VGAM833 host target gene. LOC91115 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91115, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91115 BINDING SITE, designated SEQ ID:32392, to the nucleotide sequence of VGAM833 RNA, herein designated VGAM RNA, also designated SEQ ID:3544.

[32116] Another function of VGAM833 is therefore inhibition of LOC91115 (Accession XM\_036218). Accordingly, utilities of VGAM833 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91115. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 834 (VGAM834) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32117] VGAM834 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM834 was detected is described hereinabove with reference to Figs. 1–8.

[32118] VGAM834 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus.

VGAM834 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32119] VGAM834 gene encodes a VGAM834 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM834 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM834 precursor RNA is designated SEQ ID:820, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:820 is located at position 183909 relative to the genome of Monkeypox Virus.

[32120] VGAM834 precursor RNA folds onto itself, forming VGAM834 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32121] An enzyme complex designated DICER COMPLEX, `dices` the VGAM834 folded precursor RNA into VGAM834 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM834 RNA is designated SEQ ID:3545, and is provided hereinbelow with reference to the sequence listing part.

[32122] VGAM834 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM834 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM834 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32123] VGAM834 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM834 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM834 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM834 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM834 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[32124] The complementary binding of VGAM834 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM834 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM834 host target RNA into VGAM834 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32125] It is appreciated that VGAM834 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM834 host target genes. The mRNA of each one of this plurality of VGAM834 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM834 RNA, herein designated VGAM RNA, and which when bound by VGAM834 RNA causes inhibition of translation of respective one or more VGAM834 host target proteins.

[32126] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM834 gene, herein designated VGAM GENE, on one or more VGAM834 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32127] It is yet further appreciated that a function of VGAM834 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM834 correlate with, and may be deduced from, the identity of the host target genes which VGAM834 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32128] Nucleotide sequences of the VGAM834 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM834 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM834 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM834 are further described hereinbelow with reference to Table 1.

[32129] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM834 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM834 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32130] As mentioned hereinabove with reference to Fig. 1, a function of VGAM834 gene, herein designated VGAM is inhibition of expression of VGAM834 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM834 correlate with, and may be deduced from, the identity of the target genes which VGAM834 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32131] ALG6 (Accession NM\_013339) is a VGAM834 host target gene. ALG6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ALG6, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALG6 BINDING SITE, designated SEQ ID:14987, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32132] A function of VGAM834 is therefore inhibition of ALG6 (Accession NM\_013339). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALG6. Bromodomain Adjacent to Zinc Finger Domain, 2A (BAZ2A, Accession NM\_013449) is another VGAM834 host target gene. BAZ2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BAZ2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BAZ2A BINDING SITE, designated SEQ ID:15119, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32133] Another function of VGAM834 is therefore inhibition of Bromodomain Adjacent to Zinc Finger Domain, 2A (BAZ2A, Accession NM\_013449). Accordingly, utilities of VGAM834



include diagnosis, prevention and treatment of diseases and clinical conditions associated with BAZ2A. B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633) is another VGAM834 host target gene. BCL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2 BINDING SITE, designated SEQ ID:6259, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32134] Another function of VGAM834 is therefore inhibition of B-cell CLL/lymphoma 2 (BCL2, Accession NM\_000633). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL2. N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243) is another VGAM834 host target gene. NDRG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NDRG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the

nucleotide sequences of NDRG1 BINDING SITE, designated SEQ ID:29964, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32135] Another function of VGAM834 is therefore inhibition of N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243), a gene which may have a growth inhibitory role. Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDRG1. The function of NDRG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM144. Epsin 2 (EPN2, Accession NM\_014964) is another VGAM834 host target gene. EPN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPN2 BINDING SITE, designated SEQ ID:17349, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32136] Another function of VGAM834 is therefore inhibition of Epsin 2 (EPN2, Accession NM\_014964). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPN2. FLJ31952 (Accession NM\_144682) is another VGAM834 host target gene. FLJ31952 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ31952, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ31952 BINDING SITE, designated SEQ ID:29497, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32137] Another function of VGAM834 is therefore inhibition of FLJ31952 (Accession NM\_144682). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ31952. H326 (Accession NM\_015726) is another VGAM834 host target gene. H326 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by H326, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of H326 BINDING SITE, designated SEQ ID:17937, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32138] Another function of VGAM834 is therefore inhibition of H326 (Accession NM\_015726). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with H326. Hyaluronan Binding Protein 4 (HABP4, Accession XM\_047263) is another VGAM834 host target gene. HABP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HABP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HABP4 BINDING SITE, designated SEQ ID:34925, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32139] Another function of VGAM834 is therefore inhibition of Hyaluronan Binding Protein 4 (HABP4, Accession XM\_047263). Accordingly, utilities of VGAM834 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with HABP4. KIAA0894 (Accession NM\_014896) is another VGAM834 host target gene. KIAA0894 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0894, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0894 BINDING SITE, designated SEQ ID:17054, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32140] Another function of VGAM834 is therefore inhibition of KIAA0894 (Accession NM\_014896). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0894. KIAA1157 (Accession XM\_051093) is another VGAM834 host target gene. KIAA1157 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1157, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1157 BINDING SITE, designated SEQ ID:35748, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32141] Another function of VGAM834 is therefore inhibition of KIAA1157 (Accession XM\_051093). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1157. KIAA1594 (Accession XM\_050754) is another VGAM834 host target gene. KIAA1594 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1594, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1594 BINDING SITE, designated SEQ ID:35675, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32142] Another function of VGAM834 is therefore inhibition of KIAA1594 (Accession XM\_050754). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1594. MGC12928 (Accession NM\_032891) is another VGAM834 host target gene. MGC12928 BINDING SITE is

HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGC12928, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC12928 BINDING SITE, designated SEQ ID:26714, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32143] Another function of VGAM834 is therefore inhibition of MGC12928 (Accession NM\_032891). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC12928. LOC142955 (Accession XM\_084389) is another VGAM834 host target gene. LOC142955 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC142955, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC142955 BINDING SITE, designated SEQ ID:37574, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32144] Another function of VGAM834 is therefore inhibition of

LOC142955 (Accession XM\_084389). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC142955. LOC144519 (Accession XM\_084890) is another VGAM834 host target gene. LOC144519 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144519, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144519 BINDING SITE, designated SEQ ID:37757, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32145] Another function of VGAM834 is therefore inhibition of LOC144519 (Accession XM\_084890). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144519. LOC146056 (Accession XM\_085299) is another VGAM834 host target gene. LOC146056 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-



illustrates the complementarity of the nucleotide sequences of LOC146056 BINDING SITE, designated SEQ ID:38051, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32146] Another function of VGAM834 is therefore inhibition of LOC146056 (Accession XM\_085299). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146056. LOC149153 (Accession XM\_097599) is another VGAM834 host target gene. LOC149153 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149153, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149153 BINDING SITE, designated SEQ ID:40965, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32147] Another function of VGAM834 is therefore inhibition of LOC149153 (Accession XM\_097599). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149153. LOC149420 (Accession XM\_086530) is an-

other VGAM834 host target gene. LOC149420 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149420, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149420 BINDING SITE, designated SEQ ID:38747, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32148] Another function of VGAM834 is therefore inhibition of LOC149420 (Accession XM\_086530). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149420. LOC92106 (Accession NM\_138381) is another VGAM834 host target gene. LOC92106 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92106 BINDING SITE, designated SEQ ID:28756, to the nucleotide sequence of VGAM834 RNA, herein designated VGAM RNA, also designated SEQ ID:3545.

[32149] Another function of VGAM834 is therefore inhibition of LOC92106 (Accession NM\_138381). Accordingly, utilities of VGAM834 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92106. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 835 (VGAM835) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32150] VGAM835 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM835 was detected is described hereinabove with reference to Figs. 1–8.

[32151] VGAM835 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus. VGAM835 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32152] VGAM835 gene encodes a VGAM835 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM835

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM835 precursor RNA is designated SEQ ID:821, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:821 is located at position 184176 relative to the genome of Monkeypox Virus.

[32153] VGAM835 precursor RNA folds onto itself, forming VGAM835 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32154] An enzyme complex designated DICER COMPLEX, `dices` the VGAM835 folded precursor RNA into VGAM835 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 47%) nucleotide sequence of VGAM835 RNA is designated SEQ ID:3546, and is provided hereinbelow with reference to the sequence listing part.

[32155] VGAM835 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM835 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM835 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32156] VGAM835 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM835 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM835 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM835 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM835 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32157] The complementary binding of VGAM835 RNA, herein designated VGAM RNA, to host target binding sites on VGAM835 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM835 host target RNA into VGAM835 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32158] It is appreciated that VGAM835 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM835 host target genes. The mRNA of each one of this plurality of VGAM835 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM835 RNA, herein designated VGAM RNA, and which when bound by VGAM835 RNA causes inhibition of translation of respective one or more VGAM835 host target proteins.

[32159] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM835 gene, herein designated VGAM GENE, on one or more VGAM835 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32160] It is yet further appreciated that a function of VGAM835 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM835 correlate with, and may be deduced from, the identity of the host target genes which VGAM835 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32161] Nucleotide sequences of the VGAM835 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM835 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM835 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM835 are further described hereinbelow with reference to Table 1.

[32162] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM835 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM835 RNA, herein designated VGAM RNA, are described hereinbelow with refer-



ence to Table 2.

[32163] As mentioned hereinabove with reference to Fig. 1, a function of VGAM835 gene, herein designated VGAM is inhibition of expression of VGAM835 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM835 correlate with, and may be deduced from, the identity of the target genes which VGAM835 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32164] Growth Arrest-specific 7 (GAS7, Accession NM\_003644) is a VGAM835 host target gene. GAS7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAS7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAS7 BINDING SITE, designated SEQ ID:9714, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32165] A function of VGAM835 is therefore inhibition of Growth Arrest-specific 7 (GAS7, Accession NM\_003644), a gene which may play a role in promoting maturation and morphological differentiation of cerebellar neurons. Accord-

ingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAS7. The function of GAS7 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM232.Heparan Sulfate

2-O-sulfotransferase 1 (HS2ST1, Accession NM\_012262) is another VGAM835 host target gene. HS2ST1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HS2ST1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HS2ST1 BINDING SITE, designated SEQ ID:14577, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32166] Another function of VGAM835 is therefore inhibition of Heparan Sulfate 2-O-sulfotransferase 1 (HS2ST1, Accession NM\_012262). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HS2ST1. Leucine Zipper Protein 1 (LUZP1, Accession NM\_033631) is another VGAM835 host target gene. LUZP1 BINDING SITE is HOST

TARGET binding site found in the 3` untranslated region of mRNA encoded by LUZP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LUZP1 BINDING SITE, designated SEQ ID:27351, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32167] Another function of VGAM835 is therefore inhibition of Leucine Zipper Protein 1 (LUZP1, Accession NM\_033631). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LUZP1. Synovial Sarcoma, X Breakpoint 3 (SSX3, Accession NM\_021014) is another VGAM835 host target gene. SSX3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SSX3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SSX3 BINDING SITE, designated SEQ ID:22003, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32168] Another function of VGAM835 is therefore inhibition of Synovial Sarcoma, X Breakpoint 3 (SSX3, Accession NM\_021014), a gene which could act as a modulator of transcription. Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SSX3. The function of SSX3 has been established by previous studies. By screening a testis cDNA library with a partial fragment of the SSX2 (OMIM Ref. No. 300192) gene, de Leeuw et al. (1996) identified SSX3, a novel member of the Kruppel-associated box (KRAB)-containing SSX gene family. SSX3 encodes a deduced 188-amino acid protein that shares 90% sequence identity with SSX2. Unlike SSX1 (OMIM Ref. No. 312820) and SSX2, SSX3 appears not to be involved in the chromosome translocation t(X;18)(p11.2;q11.2) commonly found in synovial sarcomas. Gure et al. (1997) independently cloned the SSX3 gene and showed that it is expressed in normal testis only. Analysis of 12 melanoma cell lines detected no expression of SSX3.

[32169] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32170] de Leeuw, B.; Balemans, M.; Geurts van Kessel, A. : A novel

Kruppel-associated box containing the SSX gene (SSX3) on the human X chromosome is not implicated in t(X;18)-positive synovial sarcomas. Cytogenet. Cell Genet. 73: 179-183, 1996. ; and

[32171] Gure, A. O.; Tureci, O.; Sahin, U.; Tsang, S.; Scanlan, M. J.; Jager, E.; Knuth, A.; Pfreundschuh, M.; Old, L. J.; Chen, Y.-T. : SSX: a multigene family with several members transcribed.

[32172] Further studies establishing the function and utilities of SSX3 are found in John Hopkins OMIM database record ID 300325, and in cited publications numbered 9146-9147 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 1 Open Reading Frame 24 (C1orf24, Accession NM\_052966) is another VGAM835 host target gene. C1orf24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1orf24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C1orf24 BINDING SITE, designated SEQ ID:27536, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32173] Another function of VGAM835 is therefore inhibition of Chromosome 1 Open Reading Frame 24 (C1orf24, Accession NM\_052966). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf24. DKFZP586C1619 (Accession XM\_030350) is another VGAM835 host target gene. DKFZP586C1619 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP586C1619, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586C1619 BINDING SITE, designated SEQ ID:31021, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32174] Another function of VGAM835 is therefore inhibition of DKFZP586C1619 (Accession XM\_030350). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586C1619. Dickkopf Homolog 2 (*Xenopus laevis*) (DKK2, Accession NM\_014421) is another VGAM835 host target gene. DKK2 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by DKK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKK2 BINDING SITE, designated SEQ ID:15773, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32175] Another function of VGAM835 is therefore inhibition of Dickkopf Homolog 2 (*Xenopus laevis*) (DKK2, Accession NM\_014421). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKK2. FLJ14213 (Accession NM\_024841) is another VGAM835 host target gene. FLJ14213 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14213, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14213 BINDING SITE, designated SEQ ID:24255, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32176] Another function of VGAM835 is therefore inhibition of FLJ14213 (Accession NM\_024841). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14213. FLJ23548 (Accession NM\_024590) is another VGAM835 host target gene. FLJ23548 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ23548, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23548 BINDING SITE, designated SEQ ID:23825, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32177] Another function of VGAM835 is therefore inhibition of FLJ23548 (Accession NM\_024590). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23548. KIAA0831 (Accession NM\_014924) is another VGAM835 host target gene. KIAA0831 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0831, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or



BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0831 BINDING SITE, designated SEQ ID:17209, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32178] Another function of VGAM835 is therefore inhibition of KIAA0831 (Accession NM\_014924). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0831. MGC13061 (Accession NM\_032322) is another VGAM835 host target gene. MGC13061 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC13061, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC13061 BINDING SITE, designated SEQ ID:26129, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32179] Another function of VGAM835 is therefore inhibition of MGC13061 (Accession NM\_032322). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

MGC13061. LOC154739 (Accession XM\_098602) is another VGAM835 host target gene. LOC154739 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC154739, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154739 BINDING SITE, designated SEQ ID:41719, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32180] Another function of VGAM835 is therefore inhibition of LOC154739 (Accession XM\_098602). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154739. LOC203276 (Accession XM\_117523) is another VGAM835 host target gene. LOC203276 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203276 BINDING SITE, designated SEQ ID:43487, to the nucleotide sequence of VGAM835 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3546.

[32181] Another function of VGAM835 is therefore inhibition of LOC203276 (Accession XM\_117523). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203276. LOC203305 (Accession XM\_117529) is another VGAM835 host target gene. LOC203305 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203305, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203305 BINDING SITE, designated SEQ ID:43511, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32182] Another function of VGAM835 is therefore inhibition of LOC203305 (Accession XM\_117529). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203305. LOC219686 (Accession XM\_165544) is another VGAM835 host target gene. LOC219686 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219686, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219686 BINDING SITE, designated SEQ ID:43675, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32183] Another function of VGAM835 is therefore inhibition of LOC219686 (Accession XM\_165544). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219686. LOC254243 (Accession XM\_173233) is another VGAM835 host target gene. LOC254243 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254243, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254243 BINDING SITE, designated SEQ ID:46514, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32184] Another function of VGAM835 is therefore inhibition of LOC254243 (Accession XM\_173233). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC254243. LOC63923 (Accession XM\_040527) is another VGAM835 host target gene. LOC63923 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC63923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC63923 BINDING SITE, designated SEQ ID:33324, to the nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32185] Another function of VGAM835 is therefore inhibition of LOC63923 (Accession XM\_040527). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC63923. LOC90038 (Accession XM\_028305) is another VGAM835 host target gene. LOC90038 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90038 BINDING SITE, designated SEQ ID:30651, to the

nucleotide sequence of VGAM835 RNA, herein designated VGAM RNA, also designated SEQ ID:3546.

[32186] Another function of VGAM835 is therefore inhibition of LOC90038 (Accession XM\_028305). Accordingly, utilities of VGAM835 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90038. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 836 (VGAM836) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32187] VGAM836 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM836 was detected is described hereinabove with reference to Figs. 1–8.

[32188] VGAM836 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus. VGAM836 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32189] VGAM836 gene encodes a VGAM836 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM836 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM836 precursor RNA is designated SEQ ID:822, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:822 is located at position 185395 relative to the genome of Monkeypox Virus.

[32190] VGAM836 precursor RNA folds onto itself, forming VGAM836 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32191] An enzyme complex designated DICER COMPLEX, `dices` the VGAM836 folded precursor RNA into VGAM836 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short

~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM836 RNA is designated SEQ ID:3547, and is provided hereinbelow with reference to the sequence listing part.

[32192] VGAM836 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM836 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM836 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32193] VGAM836 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM836 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM836 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding



sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM836 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM836 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32194] The complementary binding of VGAM836 RNA, herein designated VGAM RNA, to host target binding sites on VGAM836 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM836 host target RNA into VGAM836 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32195] It is appreciated that VGAM836 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM836 host target genes. The mRNA of each one of this plurality of VGAM836 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM836 RNA, herein designated VGAM RNA, and which when bound by VGAM836 RNA causes inhibition of translation of respective one or more VGAM836 host target proteins.

[32196] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM836 gene, herein designated VGAM GENE, on one or more VGAM836 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[32197] It is yet further appreciated that a function of VGAM836 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM836 correlate with, and may be deduced from, the identity of the host target genes which VGAM836 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[32198] Nucleotide sequences of the VGAM836 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM836 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM836 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM836 are further described hereinbelow with reference to Table 1.

[32199] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM836 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM836 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32200] As mentioned hereinabove with reference to Fig. 1, a function of VGAM836 gene, herein designated VGAM is inhibition of expression of VGAM836 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM836 correlate with, and may be deduced from, the identity of the target genes which VGAM836 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32201] Ribosomal Protein L15 (RPL15, Accession NM\_002948) is a VGAM836 host target gene. RPL15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RPL15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RPL15 BINDING SITE, designated SEQ ID:8860, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32202] A function of VGAM836 is therefore inhibition of Ribosomal Protein L15 (RPL15, Accession NM\_002948). Accord-

ingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RPL15. BRCA2 and CDKN1A Interacting Protein (BCCIP, Accession NM\_078469) is another VGAM836 host target gene. BCCIP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCCIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCCIP BINDING SITE, designated SEQ ID:27786, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32203] Another function of VGAM836 is therefore inhibition of BRCA2 and CDKN1A Interacting Protein (BCCIP, Accession NM\_078469). Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCCIP. KIAA1110 (Accession XM\_029973) is another VGAM836 host target gene. KIAA1110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1110 BINDING SITE, designated SEQ ID:30981, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32204] Another function of VGAM836 is therefore inhibition of KIAA1110 (Accession XM\_029973). Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1110. KIAA1877 (Accession XM\_038616) is another VGAM836 host target gene. KIAA1877 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1877, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1877 BINDING SITE, designated SEQ ID:32885, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32205] Another function of VGAM836 is therefore inhibition of KIAA1877 (Accession XM\_038616). Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1877. Proline-rich Gla (G-carboxyglutamic acid) Polypeptide 1 (PRRG1, Accession NM\_000950) is another VGAM836 host target gene. PRRG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRRG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRRG1 BINDING SITE, designated SEQ ID:6656, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32206] Another function of VGAM836 is therefore inhibition of Proline-rich Gla (G-carboxyglutamic acid) Polypeptide 1 (PRRG1, Accession NM\_000950). Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRRG1. LOC149910 (Accession XM\_086699) is another VGAM836 host target gene. LOC149910 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149910, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149910 BINDING

SITE, designated SEQ ID:38828, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32207] Another function of VGAM836 is therefore inhibition of LOC149910 (Accession XM\_086699). Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149910. LOC151405 (Accession XM\_098058) is another VGAM836 host target gene. LOC151405 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151405, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151405 BINDING SITE, designated SEQ ID:41338, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32208] Another function of VGAM836 is therefore inhibition of LOC151405 (Accession XM\_098058). Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151405. LOC153196 (Accession XM\_098323) is another VGAM836 host target gene. LOC153196 BINDING



SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC153196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153196 BINDING SITE, designated SEQ ID:41587, to the nucleotide sequence of VGAM836 RNA, herein designated VGAM RNA, also designated SEQ ID:3547.

[32209] Another function of VGAM836 is therefore inhibition of LOC153196 (Accession XM\_098323). Accordingly, utilities of VGAM836 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153196. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 837 (VGAM837) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32210] VGAM837 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM837 was detected is described hereinabove with reference to Figs. 1-8.

[32211] VGAM837 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus.

VGAM837 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32212] VGAM837 gene encodes a VGAM837 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM837 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM837 precursor RNA is designated SEQ ID:823, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:823 is located at position 183768 relative to the genome of Monkeypox Virus.

[32213] VGAM837 precursor RNA folds onto itself, forming VGAM837 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[32214] An enzyme complex designated DICER COMPLEX, `dices` the VGAM837 folded precursor RNA into VGAM837 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM837 RNA is designated SEQ ID:3548, and is provided hereinbelow with reference to the sequence listing part.

[32215] VGAM837 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM837 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM837 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32216] VGAM837 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM837 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM837 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM837 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM837 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32217] The complementary binding of VGAM837 RNA, herein designated VGAM RNA, to host target binding sites on VGAM837 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM837 host target RNA into VGAM837 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32218] It is appreciated that VGAM837 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM837 host target genes. The mRNA of each one of this plurality of VGAM837 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM837 RNA, herein designated VGAM RNA, and which when bound by VGAM837 RNA causes inhibition of translation of respective one or more VGAM837 host target proteins.

[32219] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM837 gene, herein designated VGAM GENE, on one or more VGAM837 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32220] It is yet further appreciated that a function of VGAM837 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM837 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM837 correlate with, and may be deduced from, the identity of the host target genes which VGAM837 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32221] Nucleotide sequences of the VGAM837 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM837 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM837 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM837 are further described hereinbelow with reference to Table 1.

[32222] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM837 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM837 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32223] As mentioned hereinabove with reference to Fig. 1, a function of VGAM837 gene, herein designated VGAM is inhibition of expression of VGAM837 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM837 correlate with, and may be deduced from, the identity of the target genes which VGAM837 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32224] Ubiquitin-like 3 (UBL3, Accession NM\_007106) is a VGAM837 host target gene. UBL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of UBL3 BINDING SITE, designated SEQ ID:13966, to the nucleotide sequence of VGAM837 RNA, herein designated VGAM RNA, also designated SEQ ID:3548.

[32225] A function of VGAM837 is therefore inhibition of Ubiquitin-like 3 (UBL3, Accession NM\_007106), a gene which appears to have a diverse range of cellular functions. Accordingly, utilities of VGAM837 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBL3. The function of UBL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM459.FLJ13611 (Accession NM\_024941) is another VGAM837 host target gene.

FLJ13611 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13611, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13611 BINDING SITE, designated SEQ ID:24485, to the nucleotide sequence of VGAM837 RNA, herein designated VGAM RNA, also designated SEQ ID:3548.



- [32226] Another function of VGAM837 is therefore inhibition of FLJ13611 (Accession NM\_024941). Accordingly, utilities of VGAM837 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13611. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 838 (VGAM838) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [32227] VGAM838 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM838 was detected is described hereinabove with reference to Figs. 1–8.
- [32228] VGAM838 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus. VGAM838 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.
- [32229] VGAM838 gene encodes a VGAM838 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM838 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM838 precursor RNA is designated SEQ ID:824, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:824 is located at position 183284 relative to the genome of Monkeypox Virus.

[32230] VGAM838 precursor RNA folds onto itself, forming VGAM838 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32231] An enzyme complex designated DICER COMPLEX, `dices` the VGAM838 folded precursor RNA into VGAM838 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide se-

quence of VGAM838 RNA is designated SEQ ID:3549, and is provided hereinbelow with reference to the sequence listing part.

[32232] VGAM838 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM838 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM838 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[32233] VGAM838 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM838 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM838 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM838 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM838 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32234] The complementary binding of VGAM838 RNA, herein designated VGAM RNA, to host target binding sites on VGAM838 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM838 host target RNA into VGAM838 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32235] It is appreciated that VGAM838 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM838 host target genes. The mRNA of each one of this plurality of VGAM838 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM838 RNA, herein designated VGAM RNA, and which when bound by VGAM838 RNA causes inhibition of translation of respective one or more VGAM838 host target proteins.

[32236] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM838 gene, herein designated VGAM GENE, on one or more VGAM838 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32237] It is yet further appreciated that a function of VGAM838 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM838 correlate with, and may be deduced from, the identity of the host target genes which VGAM838 binds and inhibits, and the function of these host target genes, as elaborated herein—below.

[32238] Nucleotide sequences of the VGAM838 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM838 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM838 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM838 are further described hereinbelow with reference to Table 1.

[32239] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM838 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM838 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32240] As mentioned hereinabove with reference to Fig. 1, a function of VGAM838 gene, herein designated VGAM is inhibition of expression of VGAM838 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM838 correlate with, and may be deduced from, the identity of the target genes which VGAM838 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32241] AXIN1 Up-regulated 1 (AXUD1, Accession NM\_033027) is a VGAM838 host target gene. AXUD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AXUD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AXUD1 BINDING SITE, designated SEQ ID:26917, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32242] A function of VGAM838 is therefore inhibition of AXIN1 Up-regulated 1 (AXUD1, Accession NM\_033027). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AXUD1. Cadherin 13, H-cadherin (heart)

(CDH13, Accession NM\_001257) is another VGAM838 host target gene. CDH13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CDH13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDH13 BINDING SITE, designated SEQ ID:6926, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32243] Another function of VGAM838 is therefore inhibition of Cadherin 13, H-cadherin (heart) (CDH13, Accession NM\_001257). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH13. Cytochrome P450, Subfamily XXVIIIB (25-hydroxyvitamin D-1-alpha-hydroxylase), Polypeptide 1 (CYP27B1, Accession NM\_000785) is another VGAM838 host target gene. CYP27B1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP27B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide



sequences of CYP27B1 BINDING SITE, designated SEQ ID:6431, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32244] Another function of VGAM838 is therefore inhibition of Cytochrome P450, Subfamily XXVII B (25-hydroxyvitamin D-1-alpha-hydroxylase), Polypeptide 1 (CYP27B1, Accession NM\_000785). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP27B1. Dishevelled Associated Activator of Morphogenesis 2 (DAAM2, Accession XM\_166434) is another VGAM838 host target gene. DAAM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DAAM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DAAM2 BINDING SITE, designated SEQ ID:44335, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32245] Another function of VGAM838 is therefore inhibition of Dishevelled Associated Activator of Morphogenesis 2

(DAAM2, Accession XM\_166434), a gene which controls cell polarity and movement during development. Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DAAM2. The function of DAAM2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. GRB2-associated Binding Protein 2 (GAB2, Accession NM\_012296) is another VGAM838 host target gene. GAB2 BINDING SITE1 and GAB2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by GAB2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAB2 BINDING SITE1 and GAB2 BINDING SITE2, designated SEQ ID:14650 and SEQ ID:27845 respectively, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32246] Another function of VGAM838 is therefore inhibition of GRB2-associated Binding Protein 2 (GAB2, Accession NM\_012296), a gene which act as adapters for transmitting various signals. Accordingly, utilities of VGAM838 in-

clude diagnosis, prevention and treatment of diseases and clinical conditions associated with GAB2. The function of GAB2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM53. Male-specific Lethal 3-like 1 (Drosophila) (MSL3L1, Accession NM\_078628) is another VGAM838 host target gene. MSL3L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSL3L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSL3L1 BINDING SITE, designated SEQ ID:27811, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32247] Another function of VGAM838 is therefore inhibition of Male-specific Lethal 3-like 1 (Drosophila) (MSL3L1, Accession NM\_078628). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSL3L1. Microsomal Triglyceride Transfer Protein (large polypeptide, 88kDa) (MTP, Accession NM\_000253) is another VGAM838

host target gene. MTP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MTP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTP BINDING SITE, designated SEQ ID:5794, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32248] Another function of VGAM838 is therefore inhibition of Microsomal Triglyceride Transfer Protein (large polypeptide, 88kDa) (MTP, Accession NM\_000253). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTP. Nitric Oxide Synthase 1 (neuronal) (NOS1, Accession NM\_000620) is another VGAM838 host target gene. NOS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NOS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NOS1 BINDING SITE, designated SEQ ID:6233, to the nucleotide sequence of VGAM838 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3549.

[32249] Another function of VGAM838 is therefore inhibition of Nitric Oxide Synthase 1 (neuronal) (NOS1, Accession NM\_000620), a gene which produces nitric oxide (no) which is a messenger molecule with diverse functions throughout the body. Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NOS1. The function of NOS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM323.PATE (Accession NM\_138294) is another VGAM838 host target gene. PATE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PATE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PATE BINDING SITE, designated SEQ ID:28708, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32250] Another function of VGAM838 is therefore inhibition of PATE (Accession NM\_138294). Accordingly, utilities of

VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PATE.

Protein Phosphatase 1, Regulatory (inhibitor) Subunit 12A (PPP1R12A, Accession NM\_002480) is another VGAM838 host target gene. PPP1R12A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1R12A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R12A BINDING SITE, designated SEQ ID:8305, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32251] Another function of VGAM838 is therefore inhibition of Protein Phosphatase 1, Regulatory (inhibitor) Subunit 12A (PPP1R12A, Accession NM\_002480), a gene which regulates the interaction of actin and myosin. Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R12A. The function of PPP1R12A has been established by previous studies. Kimura et al. (1996) demonstrated that myosin phosphatase regulates the interaction of actin (see OMIM Ref. No. 102540) and myosin

(see OMIM Ref. No. 160710) downstream of the guanosine triphosphatase Rho. Rho appears to inhibit myosin phosphatase through the action of Rho-kinase. Using the rat Mypt1 cDNA as probe, Takahashi et al. (1997) cloned a 4,855-bp cDNA for a human gene they symbolized MYPT1. Sequencing analysis showed that human MYPT1 contains 1,030 amino acids with a calculated molecular mass of approximately 115 kD. By fluorescence in situ hybridization, Kimura et al. (1996) mapped the MYPT1 gene to 12q15-q21.2. By radiation hybrid analysis, they showed that MYPT1 is located close to a highly polymorphic marker that lies between D12S350 and D12S106.

[32252] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32253] Kimura, K.; Ito, M.; Amano, M.; Chihara, K.; Fukata, Y.; Nakafuku, M.; Yamamori, B.; Feng, J.; Nakano, T.; Okawa, K.; Iwamatsu, A.; Kaibuchi, K. : Regulation of myosin phosphatase by Rho and Rho-associated kinase (Rho-kinase). Science 273: 245-248, 1996. ; and

[32254] Takahashi, N.; Ito, M.; Tanaka, J.; Nakano, T.; Kaibuchi, K.; Odai, H.; Takemura, K. : Localization of the gene coding for myosin phosphatase, target subunit 1 (MYPT1) to hu-

man chromosom.

[32255] Further studies establishing the function and utilities of PPP1R12A are found in John Hopkins OMIM database record ID 602021, and in cited publications numbered 5829–5830 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. ABLIM (Accession NM\_006720) is another VGAM838 host target gene. ABLIM BINDING SITE1 and ABLIM BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABLIM, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABLIM BINDING SITE1 and ABLIM BINDING SITE2, designated SEQ ID:13552 and SEQ ID:8119 respectively, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32256] Another function of VGAM838 is therefore inhibition of ABLIM (Accession NM\_006720). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABLIM. FLJ12768 (Accession NM\_025163) is another VGAM838 host target gene. FLJ12768 BINDING SITE is HOST TARGET



binding site found in the 3' untranslated region of mRNA encoded by FLJ12768, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12768 BINDING SITE, designated SEQ ID:24801, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32257] Another function of VGAM838 is therefore inhibition of FLJ12768 (Accession NM\_025163). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12768. FLJ14547 (Accession NM\_032804) is another VGAM838 host target gene. FLJ14547 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14547, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14547 BINDING SITE, designated SEQ ID:26558, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32258] Another function of VGAM838 is therefore inhibition of

FLJ14547 (Accession NM\_032804). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14547. FLJ22477 (Accession NM\_024735) is another VGAM838 host target gene. FLJ22477 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22477, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22477 BINDING SITE, designated SEQ ID:24076, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32259] Another function of VGAM838 is therefore inhibition of FLJ22477 (Accession NM\_024735). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22477. KIAA0227 (Accession XM\_027236) is another VGAM838 host target gene. KIAA0227 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0227, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0227 BINDING SITE, designated SEQ ID:30447, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32260] Another function of VGAM838 is therefore inhibition of KIAA0227 (Accession XM\_027236). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0227. KIAA0265 (Accession XM\_045954) is another VGAM838 host target gene. KIAA0265 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0265, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0265 BINDING SITE, designated SEQ ID:34619, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32261] Another function of VGAM838 is therefore inhibition of KIAA0265 (Accession XM\_045954). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0265. KIAA0298 (Accession XM\_084529) is another

VGAM838 host target gene. KIAA0298 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0298, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0298 BINDING SITE, designated SEQ ID:37623, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32262] Another function of VGAM838 is therefore inhibition of KIAA0298 (Accession XM\_084529). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0298. MGC4415 (Accession NM\_031484) is another VGAM838 host target gene. MGC4415 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4415, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4415 BINDING SITE, designated SEQ ID:25565, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32263] Another function of VGAM838 is therefore inhibition of MGC4415 (Accession NM\_031484). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4415. Melanoma-derived Leucine Zipper, Extra-nuclear Factor (MLZE, Accession NM\_031415) is another VGAM838 host target gene. MLZE BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MLZE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MLZE BINDING SITE, designated SEQ ID:25395, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32264] Another function of VGAM838 is therefore inhibition of Melanoma-derived Leucine Zipper, Extra-nuclear Factor (MLZE, Accession NM\_031415). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MLZE. NCE2 (Accession NM\_080678) is another VGAM838 host target gene. NCE2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by NCE2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCE2 BINDING SITE, designated SEQ ID:27972, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32265] Another function of VGAM838 is therefore inhibition of NCE2 (Accession NM\_080678). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCE2. p25 (Accession NM\_007030) is another VGAM838 host target gene. p25 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by p25, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of p25 BINDING SITE, designated SEQ ID:13889, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32266] Another function of VGAM838 is therefore inhibition of p25 (Accession NM\_007030). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with p25.

LOC149706 (Accession XM\_097718) is another VGAM838 host target gene. LOC149706 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149706, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149706 BINDING SITE, designated SEQ ID:41061, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32267] Another function of VGAM838 is therefore inhibition of LOC149706 (Accession XM\_097718). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149706. LOC150208 (Accession XM\_097841) is another VGAM838 host target gene. LOC150208 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150208, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150208 BINDING SITE, designated SEQ ID:41156, to

the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32268] Another function of VGAM838 is therefore inhibition of LOC150208 (Accession XM\_097841). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150208. LOC157653 (Accession XM\_088353) is another VGAM838 host target gene. LOC157653 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC157653, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157653 BINDING SITE, designated SEQ ID:39630, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32269] Another function of VGAM838 is therefore inhibition of LOC157653 (Accession XM\_088353). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157653. LOC221495 (Accession XM\_168136) is another VGAM838 host target gene. LOC221495 BINDING SITE is HOST TARGET binding site found in the 3' un-



translated region of mRNA encoded by LOC221495, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221495 BINDING SITE, designated SEQ ID:45057, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32270] Another function of VGAM838 is therefore inhibition of LOC221495 (Accession XM\_168136). Accordingly, utilities of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221495. LOC221747 (Accession XM\_166460) is another VGAM838 host target gene. LOC221747 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221747, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221747 BINDING SITE, designated SEQ ID:44365, to the nucleotide sequence of VGAM838 RNA, herein designated VGAM RNA, also designated SEQ ID:3549.

[32271] Another function of VGAM838 is therefore inhibition of LOC221747 (Accession XM\_166460). Accordingly, utilities

of VGAM838 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221747. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 839 (VGAM839) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32272] VGAM839 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM839 was detected is described hereinabove with reference to Figs. 1–8.

[32273] VGAM839 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM839 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32274] VGAM839 gene encodes a VGAM839 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM839 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM839 precursor RNA is designated SEQ ID:825, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:825 is located at position 208402 relative to the genome of Fowlpox Virus.

[32275] VGAM839 precursor RNA folds onto itself, forming VGAM839 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32276] An enzyme complex designated DICER COMPLEX, `dices` the VGAM839 folded precursor RNA into VGAM839 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM839 RNA is designated SEQ ID:3550, and

is provided hereinbelow with reference to the sequence listing part.

[32277] VGAM839 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM839 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM839 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32278] VGAM839 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM839 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM839 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM839 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM839 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32279] The complementary binding of VGAM839 RNA, herein designated VGAM RNA, to host target binding sites on VGAM839 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM839 host target RNA into VGAM839 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32280] It is appreciated that VGAM839 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM839 host target genes. The mRNA of each one of this plurality of VGAM839 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM839 RNA, herein designated VGAM RNA, and which when bound by VGAM839 RNA causes inhibition of translation of respective one or more VGAM839 host target proteins.

[32281] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM839 gene, herein designated VGAM GENE, on one or more VGAM839 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32282] It is yet further appreciated that a function of VGAM839 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM839 correlate with, and may be deduced from, the identity of the host target genes which VGAM839 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32283] Nucleotide sequences of the VGAM839 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM839 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM839 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM839 are further described hereinbelow with reference to Table 1.

[32284] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM839 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM839 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32285] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM839 gene, herein designated VGAM is inhibition of expression of VGAM839 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM839 correlate with, and may be deduced from, the identity of the target genes which VGAM839 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32286] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_019900) is a VGAM839 host target gene. ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABCC1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCC1 BINDING SITE1 through ABCC1 BINDING SITE3, designated SEQ ID:21281, SEQ ID:21285 and SEQ ID:11437 respectively, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32287] A function of VGAM839 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 1 (ABCC1, Accession NM\_019900), a gene which may par-



ticipate directly in the active transport of drugs into sub-cellular organelles or influence drug distribution indirectly. Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCC1. The function of ABCC1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM479. Corticotropin Releasing Hormone Receptor 2 (CRHR2, Accession NM\_001883) is another VGAM839 host target gene. CRHR2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRHR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRHR2 BINDING SITE, designated SEQ ID:7610, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32288] Another function of VGAM839 is therefore inhibition of Corticotropin Releasing Hormone Receptor 2 (CRHR2, Accession NM\_001883), a gene which is a corticotropin releasing factor receptor type II. Accordingly, utilities of

VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRHR2.

The function of CRHR2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM737.T-complex 10 (mouse) (TCP10, Accession NM\_004610) is another VGAM839 host target gene.

TCP10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TCP10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCP10 BINDING SITE, designated SEQ ID:10950, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32289] Another function of VGAM839 is therefore inhibition of T-complex 10 (mouse) (TCP10, Accession NM\_004610). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCP10. ARPP-19 (Accession NM\_006628) is another VGAM839 host target gene. ARPP-19 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by ARPP-19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARPP-19 BINDING SITE, designated SEQ ID:13422, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32290] Another function of VGAM839 is therefore inhibition of ARPP-19 (Accession NM\_006628). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARPP-19. DKFZP586C1619 (Accession XM\_030350) is another VGAM839 host target gene. DKFZP586C1619 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP586C1619, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586C1619 BINDING SITE, designated SEQ ID:31016, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32291] Another function of VGAM839 is therefore inhibition of

DKFZP586C1619 (Accession XM\_030350). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586C1619. Double C2-like Domains, Beta (DOC2B, Accession NM\_003585) is another VGAM839 host target gene. DOC2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DOC2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DOC2B BINDING SITE, designated SEQ ID:9637, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32292] Another function of VGAM839 is therefore inhibition of Double C2-like Domains, Beta (DOC2B, Accession NM\_003585). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DOC2B. HSA243666 (Accession NM\_017582) is another VGAM839 host target gene. HSA243666 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSA243666, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSA243666 BINDING SITE, designated SEQ ID:19021, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32293] Another function of VGAM839 is therefore inhibition of HSA243666 (Accession NM\_017582). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSA243666. KIAA0172 (Accession XM\_036295) is another VGAM839 host target gene. KIAA0172 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0172, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0172 BINDING SITE, designated SEQ ID:32408, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32294] Another function of VGAM839 is therefore inhibition of KIAA0172 (Accession XM\_036295). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0172. MGC15563 (Accession NM\_032876) is another VGAM839 host target gene. MGC15563 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC15563, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15563 BINDING SITE, designated SEQ ID:26698, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32295] Another function of VGAM839 is therefore inhibition of MGC15563 (Accession NM\_032876). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15563. Solute Carrier Family 39 (zinc transporter), Member 3 (SLC39A3, Accession NM\_144564) is another VGAM839 host target gene. SLC39A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC39A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC39A3

BINDING SITE, designated SEQ ID:29361, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32296] Another function of VGAM839 is therefore inhibition of Solute Carrier Family 39 (zinc transporter), Member 3 (SLC39A3, Accession NM\_144564). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC39A3. LOC145508 (Accession XM\_085158) is another VGAM839 host target gene. LOC145508 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145508, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145508 BINDING SITE, designated SEQ ID:37886, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32297] Another function of VGAM839 is therefore inhibition of LOC145508 (Accession XM\_085158). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145508. LOC220753 (Accession XM\_167549) is an-

other VGAM839 host target gene. LOC220753 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220753, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220753 BINDING SITE, designated SEQ ID:44659, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.

[32298] Another function of VGAM839 is therefore inhibition of LOC220753 (Accession XM\_167549). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220753. LOC92078 (Accession XM\_042684) is another VGAM839 host target gene. LOC92078 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92078 BINDING SITE, designated SEQ ID:33746, to the nucleotide sequence of VGAM839 RNA, herein designated VGAM RNA, also designated SEQ ID:3550.



[32299] Another function of VGAM839 is therefore inhibition of LOC92078 (Accession XM\_042684). Accordingly, utilities of VGAM839 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92078. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 840 (VGAM840) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32300] VGAM840 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM840 was detected is described hereinabove with reference to Figs. 1–8.

[32301] VGAM840 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ictalurid Herpesvirus 1. VGAM840 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32302] VGAM840 gene encodes a VGAM840 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM840

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM840 precursor RNA is designated SEQ ID:826, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:826 is located at position 53374 relative to the genome of Ictalurid Herpesvirus 1.

[32303] VGAM840 precursor RNA folds onto itself, forming VGAM840 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32304] An enzyme complex designated DICER COMPLEX, `dices` the VGAM840 folded precursor RNA into VGAM840 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 40%) nucleotide sequence of VGAM840 RNA is designated SEQ ID:3551, and is provided hereinbelow with reference to the sequence listing part.

[32305] VGAM840 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM840 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM840 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32306] VGAM840 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM840 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM840 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM840 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM840 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32307] The complementary binding of VGAM840 RNA, herein designated VGAM RNA, to host target binding sites on VGAM840 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM840 host target RNA into VGAM840 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32308] It is appreciated that VGAM840 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM840 host target genes. The mRNA of each one of this plurality of VGAM840 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM840 RNA, herein designated VGAM RNA, and which when bound by VGAM840 RNA causes inhibition of translation of respective one or more VGAM840 host target proteins.

[32309] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM840 gene, herein designated VGAM GENE, on one or more VGAM840 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32310] It is yet further appreciated that a function of VGAM840 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of viral infection by Ictalurid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM840 correlate with, and may be deduced from, the identity of the host target genes which VGAM840 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32311] Nucleotide sequences of the VGAM840 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM840 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM840 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM840 are further described hereinbelow with reference to Table 1.

[32312] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM840 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM840 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[32313] As mentioned hereinabove with reference to Fig. 1, a function of VGAM840 gene, herein designated VGAM is inhibition of expression of VGAM840 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM840 correlate with, and may be deduced from, the identity of the target genes which VGAM840 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32314] Recombination Activating Gene 1 (RAG1, Accession NM\_000448) is a VGAM840 host target gene. RAG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAG1 BINDING SITE, designated SEQ ID:6039, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32315] A function of VGAM840 is therefore inhibition of Recombination Activating Gene 1 (RAG1, Accession NM\_000448). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with RAG1. Transmembrane Protein 1 (TMEM1, Accession NM\_003274) is another VGAM840 host target gene. TMEM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TMEM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMEM1 BINDING SITE, designated SEQ ID:9289, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32316] Another function of VGAM840 is therefore inhibition of Transmembrane Protein 1 (TMEM1, Accession NM\_003274). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMEM1. Tripartite Motif-containing 8 (TRIM8, Accession NM\_030912) is another VGAM840 host target gene. TRIM8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM8 BINDING SITE,



designated SEQ ID:25180, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32317] Another function of VGAM840 is therefore inhibition of Tripartite Motif-containing 8 (TRIM8, Accession NM\_030912). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM8. DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 33 (DDX33, Accession NM\_020162) is another VGAM840 host target gene. DDX33 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DDX33, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DDX33 BINDING SITE, designated SEQ ID:21378, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32318] Another function of VGAM840 is therefore inhibition of DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 33 (DDX33, Accession NM\_020162). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with DDX33. DKFZP586M1120 (Accession NM\_031294) is another VGAM840 host target gene. DKFZP586M1120 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DKFZP586M1120, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP586M1120 BINDING SITE, designated SEQ ID:25324, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32319] Another function of VGAM840 is therefore inhibition of DKFZP586M1120 (Accession NM\_031294). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP586M1120. KIAA0237 (Accession NM\_014747) is another VGAM840 host target gene. KIAA0237 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA0237 BINDING SITE, designated SEQ ID:16442, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32320] Another function of VGAM840 is therefore inhibition of KIAA0237 (Accession NM\_014747). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0237. KIAA0711 (Accession NM\_014867) is another VGAM840 host target gene. KIAA0711 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0711, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0711 BINDING SITE, designated SEQ ID:16956, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32321] Another function of VGAM840 is therefore inhibition of KIAA0711 (Accession NM\_014867). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0711. VLCS-H1 (Accession NM\_014031) is another VGAM840 host target gene. VLCS-H1 BINDING SITE is

HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by VLCS-H1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VLCS-H1 BINDING SITE, designated SEQ ID:15261, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32322] Another function of VGAM840 is therefore inhibition of VLCS-H1 (Accession NM\_014031). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VLCS-H1. LOC147138 (Accession XM\_085717) is another VGAM840 host target gene. LOC147138 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147138, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147138 BINDING SITE, designated SEQ ID:38308, to the nucleotide sequence of VGAM840 RNA, herein designated VGAM RNA, also designated SEQ ID:3551.

[32323] Another function of VGAM840 is therefore inhibition of

LOC147138 (Accession XM\_085717). Accordingly, utilities of VGAM840 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147138. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 841 (VGAM841) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32324] VGAM841 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM841 was detected is described hereinabove with reference to Figs. 1–8.

[32325] VGAM841 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 2. VGAM841 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32326] VGAM841 gene encodes a VGAM841 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM841 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM841 precursor RNA is designated SEQ ID:827, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:827 is located at position 161925 relative to the genome of Equine Herpesvirus 2.

[32327] VGAM841 precursor RNA folds onto itself, forming VGAM841 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32328] An enzyme complex designated DICER COMPLEX, `dices` the VGAM841 folded precursor RNA into VGAM841 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide se-

quence of VGAM841 RNA is designated SEQ ID:3552, and is provided hereinbelow with reference to the sequence listing part.

[32329] VGAM841 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM841 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM841 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32330] VGAM841 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM841 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM841 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM841 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM841 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32331] The complementary binding of VGAM841 RNA, herein designated VGAM RNA, to host target binding sites on VGAM841 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM841 host target RNA into VGAM841 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32332] It is appreciated that VGAM841 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM841 host target genes. The mRNA of each one of this plurality of VGAM841 host target genes comprises one or more host target binding sites, each



having a nucleotide sequence which is at least partly complementary to VGAM841 RNA, herein designated VGAM RNA, and which when bound by VGAM841 RNA causes inhibition of translation of respective one or more VGAM841 host target proteins.

[32333] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM841 gene, herein designated VGAM GENE, on one or more VGAM841 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32334] It is yet further appreciated that a function of VGAM841 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM841 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM841 correlate with, and may be deduced from, the identity of the host target genes which VGAM841 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32335] Nucleotide sequences of the VGAM841 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM841 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM841 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM841 are further described hereinbelow with reference to Table 1.

[32336] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM841 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM841 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32337] As mentioned hereinabove with reference to Fig. 1, a function of VGAM841 gene, herein designated VGAM is inhibition of expression of VGAM841 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM841 correlate with, and may be deduced from, the identity of the target genes which VGAM841 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32338] Giant Axonal Neuropathy (gigaxonin) (GAN, Accession NM\_022041) is a VGAM841 host target gene. GAN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAN BINDING SITE, designated SEQ ID:22562, to the nucleotide sequence of VGAM841 RNA, herein designated VGAM RNA, also designated SEQ ID:3552.

[32339] A function of VGAM841 is therefore inhibition of Giant Axonal Neuropathy (gigaxonin) (GAN, Accession NM\_022041), a gene which plays an important role in neurofilament architecture. Accordingly, utilities of VGAM841 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with GAN. The function of GAN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM606. Golgi Autoantigen, Golgin Subfamily A, 4 (GOLGA4, Accession XM\_011069) is another VGAM841 host target gene. GOLGA4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GOLGA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GOLGA4 BINDING SITE, designated SEQ ID:30164, to the nucleotide sequence of VGAM841 RNA, herein designated VGAM RNA, also designated SEQ ID:3552.

[32340] Another function of VGAM841 is therefore inhibition of Golgi Autoantigen, Golgin Subfamily A, 4 (GOLGA4, Accession XM\_011069), a gene which may play a role in vesicular transport from the trans- golgi. Accordingly, utilities of VGAM841 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GOLGA4. The function of GOLGA4 has been established by previous studies. To characterize the Golgi com-

plex, Kooy et al. (1992) used serum from a Sjogren syndrome (OMIM Ref. No. 270150) patient with a high titer of anti-Golgi autoantibodies. The serum immunoprecipitated a 230-kD protein that was specifically localized to the cytosolic surface of what is probably the trans-face of the Golgi stack. The 230-kD Golgi protein appears to be a peripheral membrane component. The authors detected the 230-kD antigen in several cell types and species. By screening a HeLa cell cDNA expression library with the anti-Golgi autoantibodies, Erlich et al. (1996) identified a p230 cDNA. The 7.7-kb p230 mRNA encodes a 2,230-amino acid protein with a predicted coiled-coil structure, stabilized by heptad repeats. The p230 protein also contains a granin motif (see OMIM Ref. No. 113705). By SDS-PAGE, p230 from HeLa cells migrates as a 230-kD protein. Daigo et al. (1999) found that the trans-Golgi gene contains at least 11 exons. Independently, Fritzler et al. (1995) cloned a partial GOLGA4 cDNA using serum from a Sjogren syndrome patient. Based on its predicted molecular mass, they designated the GOLGA4 protein 'golgin-245.'

[32341] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [32342] Daigo, Y.; Isomura, M.; Nishiwaki, T.; Tamari, M.; Ishikawa, S.; Kai, M.; Murata, Y.; Takeuchi, K.; Yamane, Y.; Hayashi, R.; Minami, M.; Fujino, M. A.; Hojo, Y.; Uchiyama, I.; Takagi, T.; Nakamura, Y. : Characterization of a 1200-kb genomic segment of chromosome 3p22–p21.3. DNA Res. 6: 37–44, 1999. ; and
- [32343] Fritzler, M. J.; Lung, C.–C.; Hamel, J. C.; Griffith, K. J.; Chan, E. K. L. : Molecular characterization of golgin–245, a novel Golgi complex protein containing a granin signature. J. B.
- [32344] Further studies establishing the function and utilities of GOLGA4 are found in John Hopkins OMIM database record ID 602509, and in cited publications numbered 9037–9038, 853 and 8544 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Coenzyme Q7 Homolog, Ubiquinone (yeast) (COQ7, Accession NM\_016138) is another VGAM841 host target gene. COQ7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by COQ7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of COQ7 BINDING SITE, designated SEQ ID:18223, to the nucleotide sequence of VGAM841 RNA, herein designated VGAM RNA, also designated SEQ ID:3552.

[32345] Another function of VGAM841 is therefore inhibition of Coenzyme Q7 Homolog, Ubiquinone (yeast) (COQ7, Accession NM\_016138). Accordingly, utilities of VGAM841 include diagnosis, prevention and treatment of diseases and clinical conditions associated with COQ7. FLJ20136 (Accession NM\_017684) is another VGAM841 host target gene. FLJ20136 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20136, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20136 BINDING SITE, designated SEQ ID:19229, to the nucleotide sequence of VGAM841 RNA, herein designated VGAM RNA, also designated SEQ ID:3552.

[32346] Another function of VGAM841 is therefore inhibition of FLJ20136 (Accession NM\_017684). Accordingly, utilities of VGAM841 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20136.

G Protein-coupled Receptor 64 (GPR64, Accession NM\_005756) is another VGAM841 host target gene. GPR64 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR64, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR64 BINDING SITE, designated SEQ ID:12315, to the nucleotide sequence of VGAM841 RNA, herein designated VGAM RNA, also designated SEQ ID:3552.

[32347] Another function of VGAM841 is therefore inhibition of G Protein-coupled Receptor 64 (GPR64, Accession NM\_005756). Accordingly, utilities of VGAM841 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR64. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 842 (VGAM842) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32348] VGAM842 is a novel bioinformatically detected regulatory,



non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM842 was detected is described hereinabove with reference to Figs. 1–8.

[32349] VGAM842 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Equine Herpesvirus 2. VGAM842 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32350] VGAM842 gene encodes a VGAM842 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM842 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM842 precursor RNA is designated SEQ ID:828, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:828 is located at position 161225 relative to the genome of Equine Herpesvirus 2.

[32351] VGAM842 precursor RNA folds onto itself, forming VGAM842 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32352] An enzyme complex designated DICER COMPLEX, `dices` the VGAM842 folded precursor RNA into VGAM842 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM842 RNA is designated SEQ ID:3553, and is provided hereinbelow with reference to the sequence listing part.

[32353] VGAM842 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM842 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM842 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32354] VGAM842 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM842 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM842 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM842 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM842 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32355] The complementary binding of VGAM842 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM842 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM842 host target RNA into VGAM842 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32356] It is appreciated that VGAM842 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM842 host target genes. The mRNA of each one of this plurality of VGAM842 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM842 RNA, herein designated VGAM RNA, and which when bound by VGAM842 RNA causes inhibition of translation of respective one or more VGAM842 host target proteins.

[32357] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM842 gene, herein designated VGAM GENE, on one or more VGAM842 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32358] It is yet further appreciated that a function of VGAM842 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of viral infection by Equine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM842 correlate with, and may be deduced from, the identity of the host target genes which VGAM842 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32359] Nucleotide sequences of the VGAM842 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM842 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM842 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM842 are further described hereinbelow with reference to Table 1.

[32360] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM842 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM842 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32361] As mentioned hereinabove with reference to Fig. 1, a function of VGAM842 gene, herein designated VGAM is inhibition of expression of VGAM842 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM842 correlate with, and may be deduced from, the identity of the target genes which VGAM842 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32362] Adrenomedullin (ADM, Accession NM\_001124) is a VGAM842 host target gene. ADM BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by ADM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADM BINDING SITE, designated SEQ ID:6795, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32363] A function of VGAM842 is therefore inhibition of Adrenomedullin (ADM, Accession NM\_001124), a gene which regulates blood pressure and heart rate. Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADM. The function of ADM has been established by previous studies. Adrenomedullin, a hypotensive peptide found in human pheochromocytoma, consists of 52 amino acids, has 1 intramolecular disulfide bond, and shows slight homology with the calcitonin gene-related peptide (CGRP; 114130). It may function as a hormone in circulation control because it is found in blood in a considerable concentration. Kitamura et al. (1993) constructed a cDNA library of pheochromocytoma and isolated therefrom a cDNA clone encoding an adrenomedullin precursor. The precursor, called preproa-

drenomedullin, is 185 amino acids long. By RNA-blot analysis, human adrenomedullin mRNA was found to be highly expressed in several tissues, including adrenal medulla, cardiac ventricle, lung, and kidney, as well as pheochromocytoma. By Southern blot analyses of human/hamster somatic hybrid cell lines, Ishimitsu et al. (1994) demonstrated that the ADM gene is represented by a single locus on chromosome 11. Okazaki et al. (1996) mapped the Adm gene to the distal region of mouse chromosome 7, a region that shows syntenic homology to human 11p15-q13; the human ADM gene is probably located at 11p15.4 (van Heyningen and Jones, 1993). Animal model experiments lend further support to the function of ADM. To elucidate the functions of adrenomedullin, Caron and Smithies (2001) replaced the coding region of the Adm gene in mice with a sequence encoding enhanced green fluorescent protein while leaving the Adm promoter intact.

[32364] It is appreciated that the abovementioned animal model for ADM is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[32365] Full details of the abovementioned studies are described



in the following publications, the disclosure of which are hereby incorporated by reference:

- [32366] Kitamura, K.; Sakata, J.; Kangawa, K.; Kojima, M.; Matsuo, H.; Eto, T. : Cloning and characterization of cDNA encoding a precursor for human adrenomedullin. *Biochem. Biophys. Res. Commun.* 194: 720–725, 1993. ; and
- [32367] Caron, K. M.; Smithies, O. : Extreme hydrops fetalis and cardiovascular abnormalities in mice lacking a functional adrenomedullin gene. *Proc. Nat. Acad. Sci.* 98: 615–619, 2001.
- [32368] Further studies establishing the function and utilities of ADM are found in John Hopkins OMIM database record ID 103275, and in cited publications numbered 4298–4306 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cadherin 12, Type 2 (N-cadherin 2) (CDH12, Accession NM\_004061) is another VGAM842 host target gene. CDH12 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CDH12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDH12 BINDING SITE, designated SEQ ID:10267, to the nucleotide se-

quence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32369] Another function of VGAM842 is therefore inhibition of Cadherin 12, Type 2 (N-cadherin 2) (CDH12, Accession NM\_004061). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH12. Ceroid-lipofuscinosis, Neuronal 5 (CLN5, Accession NM\_006493) is another VGAM842 host target gene. CLN5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLN5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLN5 BINDING SITE, designated SEQ ID:13229, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32370] Another function of VGAM842 is therefore inhibition of Ceroid-lipofuscinosis, Neuronal 5 (CLN5, Accession NM\_006493). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLN5. Chemokine (C-X3-C motif) Receptor 1 (CX3CR1, Accession XM\_047502) is an-

other VGAM842 host target gene. CX3CR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CX3CR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CX3CR1 BINDING SITE, designated SEQ ID:34978, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32371] Another function of VGAM842 is therefore inhibition of Chemokine (C-X3-C motif) Receptor 1 (CX3CR1, Accession XM\_047502), a gene which mediates both the adhesive and migratory functions of fractalkine. Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CX3CR1. The function of CX3CR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM25. Mannosidase, Alpha, Class 1A, Member 1 (MAN1A1, Accession XM\_166312) is another VGAM842 host target gene. MAN1A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAN1A1, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAN1A1 BINDING SITE, designated SEQ ID:44134, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32372] Another function of VGAM842 is therefore inhibition of Mannosidase, Alpha, Class 1A, Member 1 (MAN1A1, Accession XM\_166312), a gene which removes 3 distinct mannose residues from peptide-bound Man(9)-GlcNAc(2) oligosaccharides. Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAN1A1. The function of MAN1A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM172. Protein Tyrosine Phosphatase, Receptor Type, N (PTPRN, Accession NM\_002846) is another VGAM842 host target gene. PTPRN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTPRN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of PTPRN BINDING SITE, designated SEQ ID:8735, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32373] Another function of VGAM842 is therefore inhibition of Protein Tyrosine Phosphatase, Receptor Type, N (PTPRN, Accession NM\_002846). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTPRN. Secretogranin III (SCG3, Accession NM\_013243) is another VGAM842 host target gene. SCG3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCG3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCG3 BINDING SITE, designated SEQ ID:14900, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32374] Another function of VGAM842 is therefore inhibition of Secretogranin III (SCG3, Accession NM\_013243). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with SCG3. Suppressor of Cytokine Signaling 5 (SOCS5, Accession NM\_014011) is another VGAM842 host target gene. SOCS5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SOCS5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOCS5 BINDING SITE, designated SEQ ID:15227, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32375] Another function of VGAM842 is therefore inhibition of Suppressor of Cytokine Signaling 5 (SOCS5, Accession NM\_014011). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOCS5. ABLIM (Accession NM\_002313) is another VGAM842 host target gene. ABLIM BINDING SITE1 and ABLIM BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ABLIM, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABLIM BINDING SITE1 and ABLIM

BINDING SITE2, designated SEQ ID:8118 and SEQ ID:13551 respectively, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32376] Another function of VGAM842 is therefore inhibition of ABLIM (Accession NM\_002313). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABLIM. DKFZp434O0320 (Accession XM\_097012) is another VGAM842 host target gene. DKFZp434O0320 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp434O0320, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434O0320 BINDING SITE, designated SEQ ID:40705, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32377] Another function of VGAM842 is therefore inhibition of DKFZp434O0320 (Accession XM\_097012). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with DKFZp434O0320. FLJ11040 (Accession NM\_018307) is another VGAM842 host target gene. FLJ11040 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11040 BINDING SITE, designated SEQ ID:20295, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32378] Another function of VGAM842 is therefore inhibition of FLJ11040 (Accession NM\_018307). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11040. HYPH (Accession XM\_170722) is another VGAM842 host target gene. HYPH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HYPH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HYPH BINDING SITE, designated SEQ ID:45482, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ



ID:3553.

[32379] Another function of VGAM842 is therefore inhibition of HYPH (Accession XM\_170722). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HYPH. KIAA0261 (Accession XM\_042946) is another VGAM842 host target gene. KIAA0261 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0261 BINDING SITE, designated SEQ ID:33832, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32380] Another function of VGAM842 is therefore inhibition of KIAA0261 (Accession XM\_042946). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0261. KIAA0937 (Accession XM\_166213) is another VGAM842 host target gene. KIAA0937 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0937, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0937 BINDING SITE, designated SEQ ID:44016, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32381] Another function of VGAM842 is therefore inhibition of KIAA0937 (Accession XM\_166213). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0937. KIAA1091 (Accession XM\_045750) is another VGAM842 host target gene. KIAA1091 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1091, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1091 BINDING SITE, designated SEQ ID:34541, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32382] Another function of VGAM842 is therefore inhibition of KIAA1091 (Accession XM\_045750). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1091. KIAA1576 (Accession XM\_038186) is another VGAM842 host target gene. KIAA1576 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1576, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1576 BINDING SITE, designated SEQ ID:32773, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32383] Another function of VGAM842 is therefore inhibition of KIAA1576 (Accession XM\_038186). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1576. Meningioma Expressed Antigen 6 (coiled-coil proline-rich) (MGEA6, Accession NM\_005930) is another VGAM842 host target gene. MGEA6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGEA6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGEA6 BINDING

SITE, designated SEQ ID:12561, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32384] Another function of VGAM842 is therefore inhibition of Meningioma Expressed Antigen 6 (coiled-coil proline-rich) (MGEA6, Accession NM\_005930). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGEA6. NYD-SP20 (Accession NM\_032598) is another VGAM842 host target gene. NYD-SP20 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NYD-SP20, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP20 BINDING SITE, designated SEQ ID:26329, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32385] Another function of VGAM842 is therefore inhibition of NYD-SP20 (Accession NM\_032598). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP20. Sema Domain, Seven Thrombospondin Repeats

(type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM\_003966) is another VGAM842 host target gene. SEMA5A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEMA5A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA5A BINDING SITE, designated SEQ ID:10105, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32386] Another function of VGAM842 is therefore inhibition of Sema Domain, Seven Thrombospondin Repeats (type 1 and type 1-like), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 5A (SEMA5A, Accession NM\_003966). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA5A. LOC151473 (Accession XM\_087215) is another VGAM842 host target gene. LOC151473 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151473, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151473 BINDING SITE, designated SEQ ID:39122, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32387] Another function of VGAM842 is therefore inhibition of LOC151473 (Accession XM\_087215). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151473. LOC219594 (Accession XM\_165451) is another VGAM842 host target gene. LOC219594 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219594, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219594 BINDING SITE, designated SEQ ID:43640, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32388] Another function of VGAM842 is therefore inhibition of LOC219594 (Accession XM\_165451). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC219594. LOC219673 (Accession XM\_167567) is another VGAM842 host target gene. LOC219673 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219673, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219673 BINDING SITE, designated SEQ ID:44693, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32389] Another function of VGAM842 is therefore inhibition of LOC219673 (Accession XM\_167567). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219673. LOC221466 (Accession XM\_168087) is another VGAM842 host target gene. LOC221466 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221466, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221466 BINDING SITE, designated SEQ ID:44993, to

the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32390] Another function of VGAM842 is therefore inhibition of LOC221466 (Accession XM\_168087). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221466. LOC221477 (Accession XM\_166397) is another VGAM842 host target gene. LOC221477 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221477, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221477 BINDING SITE, designated SEQ ID:44258, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32391] Another function of VGAM842 is therefore inhibition of LOC221477 (Accession XM\_166397). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221477. LOC253820 (Accession XM\_171040) is another VGAM842 host target gene. LOC253820 BINDING SITE is HOST TARGET binding site found in the 5' un-



translated region of mRNA encoded by LOC253820, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253820 BINDING SITE, designated SEQ ID:45808, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32392] Another function of VGAM842 is therefore inhibition of LOC253820 (Accession XM\_171040). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253820. LOC257282 (Accession XM\_172844) is another VGAM842 host target gene. LOC257282 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257282, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257282 BINDING SITE, designated SEQ ID:46121, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32393] Another function of VGAM842 is therefore inhibition of LOC257282 (Accession XM\_172844). Accordingly, utilities

of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257282. LOC90333 (Accession XM\_030958) is another VGAM842 host target gene. LOC90333 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC90333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90333 BINDING SITE, designated SEQ ID:31225, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32394] Another function of VGAM842 is therefore inhibition of LOC90333 (Accession XM\_030958). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90333. LOC91547 (Accession XM\_039093) is another VGAM842 host target gene. LOC91547 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC91547, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC91547 BINDING SITE, designated SEQ ID:33003, to the nucleotide sequence of VGAM842 RNA, herein designated VGAM RNA, also designated SEQ ID:3553.

[32395] Another function of VGAM842 is therefore inhibition of LOC91547 (Accession XM\_039093). Accordingly, utilities of VGAM842 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91547. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 843 (VGAM843) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32396] VGAM843 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM843 was detected is described hereinabove with reference to Figs. 1–8.

[32397] VGAM843 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus. VGAM843 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32398] VGAM843 gene encodes a VGAM843 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM843 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM843 precursor RNA is designated SEQ ID:829, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:829 is located at position 120975 relative to the genome of Monkeypox Virus.

[32399] VGAM843 precursor RNA folds onto itself, forming VGAM843 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32400] An enzyme complex designated DICER COMPLEX, `dices` the VGAM843 folded precursor RNA into VGAM843 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 78%) nucleotide sequence of VGAM843 RNA is designated SEQ ID:3554, and is provided hereinbelow with reference to the sequence listing part.

[32401] VGAM843 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM843 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM843 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32402] VGAM843 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM843 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM843 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM843 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM843 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32403] The complementary binding of VGAM843 RNA, herein designated VGAM RNA, to host target binding sites on VGAM843 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM843 host target RNA into VGAM843 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32404] It is appreciated that VGAM843 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM843 host target genes. The mRNA of each one of this plurality of VGAM843 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM843 RNA, herein designated VGAM RNA, and which when bound by VGAM843 RNA causes inhibition of translation of respective one or more VGAM843 host target proteins.

[32405] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM843 gene, herein designated VGAM GENE, on one or more VGAM843 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[32406] It is yet further appreciated that a function of VGAM843 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM843 include diagnosis, prevention and treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM843 correlate with, and may be deduced from, the identity of the host target genes which VGAM843 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32407] Nucleotide sequences of the VGAM843 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM843 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM843 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM843 are further described hereinbelow with reference to Table 1.

[32408] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM843 host target RNA, and schematic



representation of the complementarity of each of these host target binding sites to VGAM843 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32409] As mentioned hereinabove with reference to Fig. 1, a function of VGAM843 gene, herein designated VGAM is inhibition of expression of VGAM843 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM843 correlate with, and may be deduced from, the identity of the target genes which VGAM843 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32410] Butyrylcholinesterase (BCHE, Accession NM\_000055) is a VGAM843 host target gene. BCHE BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BCHE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCHE BINDING SITE, designated SEQ ID:5512, to the nucleotide sequence of VGAM843 RNA, herein designated VGAM RNA, also designated SEQ ID:3554.

[32411] A function of VGAM843 is therefore inhibition of Butyryl-

cholinesterase (BCHE, Accession NM\_000055). Accordingly, utilities of VGAM843 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCHE. Ankyrin Repeat Domain 6 (ANKRD6, Accession NM\_014942) is another VGAM843 host target gene. ANKRD6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ANKRD6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANKRD6 BINDING SITE, designated SEQ ID:17250, to the nucleotide sequence of VGAM843 RNA, herein designated VGAM RNA, also designated SEQ ID:3554.

[32412] Another function of VGAM843 is therefore inhibition of Ankyrin Repeat Domain 6 (ANKRD6, Accession NM\_014942). Accordingly, utilities of VGAM843 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANKRD6. CSE-C (Accession XM\_166163) is another VGAM843 host target gene. CSE-C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CSE-C, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CSE-C BINDING SITE, designated SEQ ID:43979, to the nucleotide sequence of VGAM843 RNA, herein designated VGAM RNA, also designated SEQ ID:3554.

[32413] Another function of VGAM843 is therefore inhibition of CSE-C (Accession XM\_166163). Accordingly, utilities of VGAM843 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CSE-C. LOC145009 (Accession XM\_016472) is another VGAM843 host target gene. LOC145009 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145009, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145009 BINDING SITE, designated SEQ ID:30262, to the nucleotide sequence of VGAM843 RNA, herein designated VGAM RNA, also designated SEQ ID:3554.

[32414] Another function of VGAM843 is therefore inhibition of LOC145009 (Accession XM\_016472). Accordingly, utilities of VGAM843 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC145009. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 844 (VGAM844) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32415] VGAM844 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM844 was detected is described hereinabove with reference to Figs. 1–8.

[32416] VGAM844 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Monkeypox Virus. VGAM844 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32417] VGAM844 gene encodes a VGAM844 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM844 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM844 precursor RNA is designated SEQ ID:830, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:830 is located at position 121671 relative to the genome of Monkeypox Virus.

[32418] VGAM844 precursor RNA folds onto itself, forming VGAM844 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32419] An enzyme complex designated DICER COMPLEX, `dices` the VGAM844 folded precursor RNA into VGAM844 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 53%) nucleotide sequence of VGAM844 RNA is designated SEQ ID:3555, and is provided hereinbelow with reference to the sequence listing part.

[32420] VGAM844 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM844 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM844 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32421] VGAM844 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM844 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM844 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM844 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM844 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32422] The complementary binding of VGAM844 RNA, herein designated VGAM RNA, to host target binding sites on VGAM844 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM844 host target RNA into VGAM844 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32423] It is appreciated that VGAM844 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM844 host target genes. The mRNA of each one of this plurality of VGAM844 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM844 RNA, herein designated VGAM RNA, and which when bound by VGAM844 RNA causes in-

hibition of translation of respective one or more VGAM844 host target proteins.

[32424] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM844 gene, herein designated VGAM GENE, on one or more VGAM844 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32425] It is yet further appreciated that a function of VGAM844 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM844 include diagnosis, prevention and



treatment of viral infection by Monkeypox Virus. Specific functions, and accordingly utilities, of VGAM844 correlate with, and may be deduced from, the identity of the host target genes which VGAM844 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [32426] Nucleotide sequences of the VGAM844 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM844 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM844 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM844 are further described hereinbelow with reference to Table 1.
- [32427] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM844 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM844 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [32428] As mentioned hereinabove with reference to Fig. 1, a function of VGAM844 gene, herein designated VGAM is inhibition of expression of VGAM844 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM844 correlate with, and may be deduced from, the identity of the target genes which VGAM844 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32429] LATS, Large Tumor Suppressor, Homolog 1 (Drosophila) (LATS1, Accession XM\_015547) is a VGAM844 host target gene. LATS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LATS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LATS1 BINDING SITE, designated SEQ ID:30237, to the nucleotide sequence of VGAM844 RNA, herein designated VGAM RNA, also designated SEQ ID:3555.

[32430] A function of VGAM844 is therefore inhibition of LATS, Large Tumor Suppressor, Homolog 1 (Drosophila) (LATS1, Accession XM\_015547). Accordingly, utilities of VGAM844 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LATS1. SCDGF-B (Accession NM\_025208) is another VGAM844 host target gene. SCDGF-B BINDING SITE1 and SCDGF-B BINDING

SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SCDGF-B, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCDGF-B BINDING SITE1 and SCDGF-B BINDING SITE2, designated SEQ ID:24877 and SEQ ID:26979 respectively, to the nucleotide sequence of VGAM844 RNA, herein designated VGAM RNA, also designated SEQ ID:3555.

[32431] Another function of VGAM844 is therefore inhibition of SCDGF-B (Accession NM\_025208). Accordingly, utilities of VGAM844 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCDGF-B. Serologically Defined Colon Cancer Antigen 1 (SDCCAG1, Accession NM\_004713) is another VGAM845 host target gene. SDCCAG1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDCCAG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDCCAG1 BINDING SITE, designated SEQ ID:11069, to the nucleotide sequence of VGAM845 RNA, herein designated VGAM RNA, also designated SEQ

ID:3556.

[32432] Another function of VGAM845 is therefore inhibition of Serologically Defined Colon Cancer Antigen 1 (SDCCAG1, Accession NM\_004713). Accordingly, utilities of VGAM845 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDCCAG1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 846 (VGAM846) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32433] VGAM846 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM846 was detected is described hereinabove with reference to Figs. 1–8.

[32434] VGAM846 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM846 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32435] VGAM846 gene encodes a VGAM846 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM846 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM846 precursor RNA is designated SEQ ID:832, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:832 is located at position 132582 relative to the genome of Gallid Herpesvirus 2.

[32436] VGAM846 precursor RNA folds onto itself, forming VGAM846 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32437] An enzyme complex designated DICER COMPLEX, `dices` the VGAM846 folded precursor RNA into VGAM846 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 60%) nucleotide sequence of VGAM846 RNA is designated SEQ ID:3557, and is provided hereinbelow with reference to the sequence listing part.

[32438] VGAM846 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM846 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM846 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[32439] VGAM846 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM846 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM846 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM846 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM846 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32440] The complementary binding of VGAM846 RNA, herein designated VGAM RNA, to host target binding sites on VGAM846 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM846 host target RNA into VGAM846 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32441] It is appreciated that VGAM846 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM846 host target genes. The mRNA of

each one of this plurality of VGAM846 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM846 RNA, herein designated VGAM RNA, and which when bound by VGAM846 RNA causes inhibition of translation of respective one or more VGAM846 host target proteins.

[32442] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM846 gene, herein designated VGAM GENE, on one or more VGAM846 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science



294,779 (2001)).

[32443] It is yet further appreciated that a function of VGAM846 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM846 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM846 correlate with, and may be deduced from, the identity of the host target genes which VGAM846 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32444] Nucleotide sequences of the VGAM846 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM846 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM846 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM846 are further described hereinbelow with reference to Table 1.

[32445] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM846 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM846 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[32446] As mentioned hereinabove with reference to Fig. 1, a function of VGAM846 gene, herein designated VGAM is inhibition of expression of VGAM846 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM846 correlate with, and may be deduced from, the identity of the target genes which VGAM846 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32447] Aconitase 1, Soluble (ACO1, Accession NM\_002197) is a VGAM846 host target gene. ACO1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ACO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACO1 BINDING SITE, designated SEQ ID:7953, to the nucleotide sequence of VGAM846 RNA, herein designated VGAM RNA, also designated SEQ ID:3557.

[32448] A function of VGAM846 is therefore inhibition of Aconitase 1, Soluble (ACO1, Accession NM\_002197), a gene which an iron-dependent enzyme; catalyzes conversion of

citrate to cis-aconitate in the TCA cycle. Accordingly, utilities of VGAM846 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACO1. The function of ACO1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM53. Annexin A7 (ANXA7, Accession NM\_004034) is another VGAM846 host target gene. ANXA7 BINDING SITE1 and ANXA7 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ANXA7, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANXA7 BINDING SITE1 and ANXA7 BINDING SITE2, designated SEQ ID:10253 and SEQ ID:6824 respectively, to the nucleotide sequence of VGAM846 RNA, herein designated VGAM RNA, also designated SEQ ID:3557.

[32449] Another function of VGAM846 is therefore inhibition of Annexin A7 (ANXA7, Accession NM\_004034), a gene which promotes membrane fusion and is involved in exocytosis. Accordingly, utilities of VGAM846 include diagnosis, prevention and treatment of diseases and clinical con-

ditions associated with ANXA7. The function of ANXA7 has been established by previous studies. The ANX7 gene is located on chromosome 10q21, a site long hypothesized to harbor a tumor suppressor gene or genes associated with prostate and other cancers. To test this hypothesis, Srivastava et al. (2001) analyzed the action of the ANX7 gene on colony formation by human tumor cell lines. They also examined the expression of the ANX7 protein in a large number of prostate cancers using tumor tissue microarray technology. Finally, they tested a panel of primary and metastatic prostate cancers for evidence of loss of heterozygosity (LOH). They found that human tumor cell proliferation and colony formation were markedly reduced when the wildtype ANX7 gene was transfected into 2 prostate tumor cell lines. Consistently, analysis of ANX7 protein expression in human prostate tumor microarrays revealed a significantly higher rate of loss of ANX7 expression in metastatic and local recurrences of hormone refractory prostate cancer as compared with primary tumors ( $P = 0.0001$ ). Using 4 microsatellite markers at or near the ANX7 locus and laser capture microdissected tumor cells, 35% of 20 primary prostate tumors showed LOH. The microsatellite marker closest to the

ANX7 locus showed the highest rate of LOH, including 1 homozygous deletion. Srivastava et al. (2001) concluded that the ANX7 gene exhibits many biologic and genetic properties expected of a tumor suppressor gene and may play a role in prostate cancer progression. Animal model experiments lend further support to the function of ANXA7. By gene targeting, Srivastava et al. (1999) developed Anxa7-null mice. The null phenotype was lethal at embryonic day 10. Heterozygous mice were viable and fertile, but showed a defect in insulin secretion and an increased insulin content within isolated pancreatic islets. Electrooptical recordings suggested that the mutation altered  $\text{Ca}^{2+}$  release by agonists of inositol trisphosphate. Using mice with a different genetic background and an alternate strategy to introduce the null mutation, Herr et al. (2001) developed Anxa7  $-/-$  mice that were viable, fertile, and showed no obvious defects. Analysis of insulin secretion from isolated islets revealed no evidence for the involvement of Anxa7 in  $\text{Ca}^{2+}$ -dependent or cAMP-mediated exocytosis. In cardiomyocytes, however, they found a functional role for Anxa7 in electromechanical coupling. Cardiomyocytes from embryonic Anxa7-null mice displayed intact  $\text{Ca}^{2+}$  homeostasis and unremark-

able excitation–contraction coupling; however, adult Anxa7  $-/-$  mice exhibited a decrease in frequency–induced cell shortening.

[32450] It is appreciated that the abovementioned animal model for ANXA7 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[32451] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32452] Srivastava, M.; Atwater, I.; Glasman, M.; Leighton, X.; Goping, G.; Caohuy, H.; Miller, G.; Pichel, J.; Westphal, H.; Mears, D.; Rojas, E.; Pollard, H. B. : Defects in inositol 1,4,5–trisphosphate receptor expression,  $Ca^{2+}$  signaling, and insulin secretion in the anx7(+/-) knockout mouse. Proc. Nat. Acad. Sci. 96: 13783–13788, 1999. ; and

[32453] Srivastava, M.; Bubendorf, L.; Srikantan, V.; Fossom, L.; Nolan, L.; Glasman, M.; Leighton, X.; Fehrle, W.; Pittaluga, S.; Raffeld, M.; Koivisto, P.; Willi, N.; Gasser, T. C.; Kononen.

[32454] Further studies establishing the function and utilities of ANXA7 are found in John Hopkins OMIM database record

ID 186360, and in cited publications numbered 10507–10514 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA1729 (Accession XM\_114418) is another VGAM846 host target gene. KIAA1729 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1729, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1729 BINDING SITE, designated SEQ ID:42946, to the nucleotide sequence of VGAM846 RNA, herein designated VGAM RNA, also designated SEQ ID:3557.

[32455] Another function of VGAM846 is therefore inhibition of KIAA1729 (Accession XM\_114418). Accordingly, utilities of VGAM846 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1729. PRO1575 (Accession NM\_014092) is another VGAM846 host target gene. PRO1575 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO1575, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of PRO1575 BINDING SITE, designated SEQ ID:15311, to the nucleotide sequence of VGAM846 RNA, herein designated VGAM RNA, also designated SEQ ID:3557.

[32456] Another function of VGAM846 is therefore inhibition of PRO1575 (Accession NM\_014092). Accordingly, utilities of VGAM846 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO1575. LOC51339 (Accession NM\_016651) is another VGAM846 host target gene. LOC51339 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51339, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51339 BINDING SITE, designated SEQ ID:18767, to the nucleotide sequence of VGAM846 RNA, herein designated VGAM RNA, also designated SEQ ID:3557.

[32457] Another function of VGAM846 is therefore inhibition of LOC51339 (Accession NM\_016651). Accordingly, utilities of VGAM846 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51339. Fig. 1 further provides a conceptual descrip-



tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 847 (VGAM847) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32458] VGAM847 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM847 was detected is described hereinabove with reference to Figs. 1–8.

[32459] VGAM847 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM847 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32460] VGAM847 gene encodes a VGAM847 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM847 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM847 precursor RNA is designated SEQ ID:833, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:833 is

located at position 132873 relative to the genome of Gal-  
lid Herpesvirus 2.

[32461] VGAM847 precursor RNA folds onto itself, forming VGAM847 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32462] An enzyme complex designated DICER COMPLEX, `dices` the VGAM847 folded precursor RNA into VGAM847 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM847 RNA is designated SEQ ID:3558, and is provided hereinbelow with reference to the sequence listing part.

[32463] VGAM847 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM847 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM847 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32464] VGAM847 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM847 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM847 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM847 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM847 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[32465] The complementary binding of VGAM847 RNA, herein designated VGAM RNA, to host target binding sites on VGAM847 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM847 host target RNA into VGAM847 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32466] It is appreciated that VGAM847 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM847 host target genes. The mRNA of each one of this plurality of VGAM847 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM847 RNA, herein designated VGAM RNA, and which when bound by VGAM847 RNA causes inhibition of translation of respective one or more VGAM847

host target proteins.

[32467] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM847 gene, herein designated VGAM GENE, on one or more VGAM847 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32468] It is yet further appreciated that a function of VGAM847 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Spe-

cific functions, and accordingly utilities, of VGAM847 correlate with, and may be deduced from, the identity of the host target genes which VGAM847 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32469] Nucleotide sequences of the VGAM847 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM847 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM847 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM847 are further described hereinbelow with reference to Table 1.

[32470] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM847 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM847 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32471] As mentioned hereinabove with reference to Fig. 1, a function of VGAM847 gene, herein designated VGAM is inhibition of expression of VGAM847 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM847 correlate with, and may be deduced from, the identity of the target genes which VGAM847 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32472] ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3 (ABCC3, Accession NM\_020038) is a VGAM847 host target gene. ABCC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABCC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCC3 BINDING SITE, designated SEQ ID:21291, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32473] A function of VGAM847 is therefore inhibition of ATP-binding Cassette, Sub-family C (CFTR/MRP), Member 3 (ABCC3, Accession NM\_020038), a gene which may act as an inducible transporter in the biliary and intestinal excretion of organic anions. Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABCC3. The function of ABCC3 and its association with various

diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM505. Activin A Receptor, Type IB (ACVR1B, Accession NM\_004302) is another VGAM847 host target gene. ACVR1B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ACVR1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACVR1B BINDING SITE, designated SEQ ID:10512, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32474] Another function of VGAM847 is therefore inhibition of Activin A Receptor, Type IB (ACVR1B, Accession NM\_004302), a gene which Activin receptor-like kinase; similar to activin, TGF-beta, and C. elegans daf-1 receptors. Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACVR1B. The function of ACVR1B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM208.BLTR2



(Accession NM\_019839) is another VGAM847 host target gene. BLTR2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by BLTR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLTR2 BINDING SITE, designated SEQ ID:21246, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32475] Another function of VGAM847 is therefore inhibition of BLTR2 (Accession NM\_019839). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLTR2. Immunoglobulin Superfamily, Member 8 (IGSF8, Accession NM\_052868) is another VGAM847 host target gene. IGSF8 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by IGSF8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IGSF8 BINDING SITE, designated SEQ ID:27449, to the nucleotide sequence of VGAM847 RNA, herein designated

VGAM RNA, also designated SEQ ID:3558.

[32476] Another function of VGAM847 is therefore inhibition of Immunoglobulin Superfamily, Member 8 (IGSF8, Accession NM\_052868), a gene which inhibits the binding of prostaglandin f2-alpha to its specific fp receptor. Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IGSF8. The function of IGSF8 has been established by previous studies. Tetraspanins, such as CD81 (OMIM Ref. No. 186845), have 4 transmembrane domains and N- and C-terminal cytoplasmic regions and form extensive complexes, or webs, with other tetraspanins as well as with integrins, MHC molecules, and other proteins. The IGSF8 gene encodes a protein that forms highly proximal, specific, and stoichiometric complexes with CD81 and CD9 (OMIM Ref. No. 143030). By Brij-97 detergent lysis of a T cell line and immunoprecipitation with anti-CD81, micropeptide sequencing of the 75-kD protein, MALDI-TOF mass spectrometry, and PSD analysis, followed by database searching, Clark et al. (2001) obtained a cDNA encoding mouse Pgri ('prostaglandin regulatory-like') and the amino acid sequence of human PGRL (IGSF8). Sequence analysis predicted that the 613-amino acid Ig

superfamily protein, 90% identical to the mouse protein, possesses an N-terminal signal sequence, 4 Ig domains, 3 N-linked glycosylation sites, a transmembrane domain, and a short cytoplasmic tail. Genomic database analysis clustered PGRL into a family of proteins including IGSF2 (OMIM Ref. No. 604516), IGSF3 (OMIM Ref. No. 603491), and FPRP (OMIM Ref. No. 601204). Immunoprecipitation and mutation analysis indicated that CD81 interacts with PGRL containing all 4 Ig domains. Using Brij-96 detergent lysis of teratocarcinoma, embryonic kidney, and epithelial carcinoma cell lines and immunoprecipitation with anti-CD81, micropeptide sequencing of a 70-kD protein, and EST database searching, Stipp et al. (2001) isolated a cDNA encoding IGSF8, which they referred to as EWI2 ('glutamine-tryptophan-isoleucine-2'). Northern blot analysis of human tissues revealed expression of a 2.4-kb transcript with highest expression in brain, kidney, liver, and placenta, moderate expression in other tissues, and minimal expression in peripheral blood leukocytes. Immunoprecipitation and immunoblot analysis indicated that IGSF8, like FPRP, specifically associates highly stoichiometrically with CD81 and CD9, but not with other tetraspanins or integrins. Stipp et al. (2001) proposed that

IGSF8 may be a necessary cofactor for other CD9 and CD81 functions such as sperm-egg fusion or hepatitis C virus receptor function.

[32477] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32478] Clark, K. L; Zeng, Z.; Langford, A. L; Bowen, S. M; Todd, S. C. : PGRL is a major CD81-associated protein on lymphocytes and distinguishes a new family of cell surface proteins. J. Immun. 167: 5115-5121, 2001. ; and

[32479] Stipp, C. S.; Kolesnikova, T. V.; Hemler, M. E. : EWI-2 is a major CD9 and CD81 partner and member of a novel Ig protein subfamily. J. Biol. Chem. 276: 40545-40554, 2001.

[32480] Further studies establishing the function and utilities of IGSF8 are found in John Hopkins OMIM database record ID 606644, and in cited publications numbered 6125-6126 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Lipin 1 (LPIN1, Accession XM\_041136) is another VGAM847 host target gene. LPIN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LPIN1, corresponding to a HOST TARGET binding site such

as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LPIN1 BINDING SITE, designated SEQ ID:33469, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32481] Another function of VGAM847 is therefore inhibition of Lipin 1 (LPIN1, Accession XM\_041136), a gene which is involved in adipocyte differentiation (by similarity). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LPIN1. The function of LPIN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM35.SH3-domain Binding Protein 4 (SH3BP4, Accession NM\_014521) is another VGAM847 host target gene. SH3BP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SH3BP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SH3BP4 BINDING SITE, designated SEQ ID:15854, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3558.

[32482] Another function of VGAM847 is therefore inhibition of SH3-domain Binding Protein 4 (SH3BP4, Accession NM\_014521), a gene which is of unknown function, contains SH3-domain binding protein 4; similar to the EH-binding protein. Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SH3BP4. The function of SH3BP4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362) is another VGAM847 host target gene. TIMP3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIMP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIMP3 BINDING SITE, designated SEQ ID:5925, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32483] Another function of VGAM847 is therefore inhibition of

Tissue Inhibitor of Metalloproteinase 3 (Sorsby fundus dystrophy, pseudoinflammatory) (TIMP3, Accession NM\_000362). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIMP3. AFAP (Accession NM\_021638) is another VGAM847 host target gene. AFAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AFAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AFAP BINDING SITE, designated SEQ ID:22292, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32484] Another function of VGAM847 is therefore inhibition of AFAP (Accession NM\_021638). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AFAP. ADP-ribosylation Factor Domain Protein 1, 64kDa (ARFD1, Accession NM\_001656) is another VGAM847 host target gene. ARFD1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARFD1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARFD1 BINDING SITE, designated SEQ ID:7373, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32485] Another function of VGAM847 is therefore inhibition of ADP-ribosylation Factor Domain Protein 1, 64kDa (ARFD1, Accession NM\_001656). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARFD1. ARNTL2 (Accession NM\_020183) is another VGAM847 host target gene. ARNTL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARNTL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARNTL2 BINDING SITE, designated SEQ ID:21417, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32486] Another function of VGAM847 is therefore inhibition of ARNTL2 (Accession NM\_020183). Accordingly, utilities of



VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARNTL2. Cytochrome P450, Subfamily IIS, Polypeptide 1 (CYP2S1, Accession NM\_030622) is another VGAM847 host target gene. CYP2S1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CYP2S1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP2S1 BINDING SITE, designated SEQ ID:24964, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32487] Another function of VGAM847 is therefore inhibition of Cytochrome P450, Subfamily IIS, Polypeptide 1 (CYP2S1, Accession NM\_030622). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP2S1. F-box Only Protein 26 (FBXO26, Accession NM\_024907) is another VGAM847 host target gene. FBXO26 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FBXO26, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO26 BINDING SITE, designated SEQ ID:24404, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32488] Another function of VGAM847 is therefore inhibition of F-box Only Protein 26 (FBXO26, Accession NM\_024907). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXO26. FLJ12587 (Accession NM\_022480) is another VGAM847 host target gene. FLJ12587 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12587, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12587 BINDING SITE, designated SEQ ID:22853, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32489] Another function of VGAM847 is therefore inhibition of FLJ12587 (Accession NM\_022480). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12587.

FLJ20174 (Accession NM\_017699) is another VGAM847 host target gene. FLJ20174 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ20174, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20174 BINDING SITE, designated SEQ ID:19272, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32490] Another function of VGAM847 is therefore inhibition of FLJ20174 (Accession NM\_017699). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20174. KIAA1396 (Accession XM\_032054) is another VGAM847 host target gene. KIAA1396 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1396, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1396 BINDING SITE, designated SEQ ID:31548, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3558.

[32491] Another function of VGAM847 is therefore inhibition of KIAA1396 (Accession XM\_032054). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1396. MGC2752 (Accession XM\_085842) is another VGAM847 host target gene. MGC2752 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGC2752, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2752 BINDING SITE, designated SEQ ID:38369, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32492] Another function of VGAM847 is therefore inhibition of MGC2752 (Accession XM\_085842). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2752. Neurexophilin 3 (NXPH3, Accession XM\_037847) is another VGAM847 host target gene. NXPH3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by

NXPH3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NXPH3 BINDING SITE, designated SEQ ID:32716, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32493] Another function of VGAM847 is therefore inhibition of Neurexophilin 3 (NXPH3, Accession XM\_037847). Accordingly, utilities of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NXPH3. LOC145501 (Accession XM\_085157) is another VGAM847 host target gene. LOC145501 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145501, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145501 BINDING SITE, designated SEQ ID:37885, to the nucleotide sequence of VGAM847 RNA, herein designated VGAM RNA, also designated SEQ ID:3558.

[32494] Another function of VGAM847 is therefore inhibition of LOC145501 (Accession XM\_085157). Accordingly, utilities

of VGAM847 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145501. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 848 (VGAM848) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32495] VGAM848 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM848 was detected is described hereinabove with reference to Figs. 1–8.

[32496] VGAM848 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM848 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32497] VGAM848 gene encodes a VGAM848 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM848 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM848 precursor RNA is designated SEQ ID:834, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:834 is located at position 132736 relative to the genome of Gallid Herpesvirus 2.

[32498] VGAM848 precursor RNA folds onto itself, forming VGAM848 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32499] An enzyme complex designated DICER COMPLEX, `dices` the VGAM848 folded precursor RNA into VGAM848 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 47%) nucleotide sequence of VGAM848 RNA is designated SEQ ID:3559, and

is provided hereinbelow with reference to the sequence listing part.

[32500] VGAM848 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM848 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM848 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32501] VGAM848 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM848 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM848 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-



ing – VGAM848 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM848 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32502] The complementary binding of VGAM848 RNA, herein designated VGAM RNA, to host target binding sites on VGAM848 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM848 host target RNA into VGAM848 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32503] It is appreciated that VGAM848 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM848 host target genes. The mRNA of each one of this plurality of VGAM848 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM848 RNA, herein designated VGAM RNA, and which when bound by VGAM848 RNA causes inhibition of translation of respective one or more VGAM848 host target proteins.

[32504] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM848 gene, herein designated VGAM GENE, on one or more VGAM848 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32505] It is yet further appreciated that a function of VGAM848 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM848 correlate with, and may be deduced from, the identity of the host target genes which VGAM848 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32506] Nucleotide sequences of the VGAM848 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM848 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM848 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM848 are further described hereinbelow with reference to Table 1.

[32507] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM848 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM848 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32508] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM848 gene, herein designated VGAM is inhibition of expression of VGAM848 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM848 correlate with, and may be deduced from, the identity of the target genes which VGAM848 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32509] Carcinoembryonic Antigen-related Cell Adhesion Molecule 1 (biliary glycoprotein) (CEACAM1, Accession NM\_001712) is a VGAM848 host target gene. CEACAM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CEACAM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CEACAM1 BINDING SITE, designated SEQ ID:7439, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32510] A function of VGAM848 is therefore inhibition of Carcinoembryonic Antigen-related Cell Adhesion Molecule 1 (biliary glycoprotein) (CEACAM1, Accession NM\_001712), a gene which is a major effector of VEGF and may be a target for the inhibition of tumor angiogenesis. Accord-

ingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CEACAM1. The function of CEACAM1 and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM93. Erythrocyte Membrane Protein Band 4.9 (dematin) (EPB49, Accession NM\_001978) is another VGAM848 host target gene. EPB49 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPB49, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPB49 BINDING SITE, designated SEQ ID:7707, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32511] Another function of VGAM848 is therefore inhibition of Erythrocyte Membrane Protein Band 4.9 (dematin) (EPB49, Accession NM\_001978), a gene which is an actin-bundling protein. Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPB49. The function of EPB49 and its association with various diseases and clinical con-

ditions, has been established by previous studies, as described hereinabove with reference to VGAM760. Mannosyl (alpha-1,6-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession NM\_002408) is another VGAM848 host target gene. MGAT2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGAT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGAT2 BINDING SITE, designated SEQ ID:8230, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32512] Another function of VGAM848 is therefore inhibition of Mannosyl (alpha-1,6-)-glycoprotein Beta-1,2-N-acetylglucosaminyltransferase (MGAT2, Accession NM\_002408). Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGAT2. Pleckstrin Homology-like Domain, Family A, Member 3 (PHLDA3, Accession NM\_012396) is another VGAM848 host target gene. PHLDA3 BINDING SITE is HOST TARGET binding site found

in the 3` untranslated region of mRNA encoded by PHLDA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PHLDA3 BINDING SITE, designated SEQ ID:14758, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32513] Another function of VGAM848 is therefore inhibition of Pleckstrin Homology-like Domain, Family A, Member 3 (PHLDA3, Accession NM\_012396). Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PHLDA3. DRCTNNB1A (Accession NM\_032581) is another VGAM848 host target gene. DRCTNNB1A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DRCTNNB1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DRCTNNB1A BINDING SITE, designated SEQ ID:26315, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32514] Another function of VGAM848 is therefore inhibition of DRCTNNB1A (Accession NM\_032581). Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DRCTNNB1A. KIAA0876 (Accession XM\_035625) is another VGAM848 host target gene. KIAA0876 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0876, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0876 BINDING SITE, designated SEQ ID:32292, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32515] Another function of VGAM848 is therefore inhibition of KIAA0876 (Accession XM\_035625). Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0876. I(3)mbt-like 2 (Drosophila) (L3MBTL2, Accession XM\_114201) is another VGAM848 host target gene. L3MBTL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by L3MBTL2, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of L3MBTL2 BINDING SITE, designated SEQ ID:42786, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32516] Another function of VGAM848 is therefore inhibition of l(3)mbt-like 2 (Drosophila) (L3MBTL2, Accession XM\_114201). Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with L3MBTL2. Ornithine Decarboxylase Antizyme Inhibitor (OAZIN, Accession NM\_015878) is another VGAM848 host target gene. OAZIN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OAZIN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of OAZIN BINDING SITE, designated SEQ ID:18019, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32517] Another function of VGAM848 is therefore inhibition of

Ornithine Decarboxylase Antizyme Inhibitor (OAZIN, Accession NM\_015878). Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OAZIN. LOC146336 (Accession XM\_085421) is another VGAM848 host target gene. LOC146336 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146336, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146336 BINDING SITE, designated SEQ ID:38132, to the nucleotide sequence of VGAM848 RNA, herein designated VGAM RNA, also designated SEQ ID:3559.

[32518] Another function of VGAM848 is therefore inhibition of LOC146336 (Accession XM\_085421). Accordingly, utilities of VGAM848 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146336. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 849 (VGAM849) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[32519] VGAM849 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM849 was detected is described hereinabove with reference to Figs. 1–8.

[32520] VGAM849 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM849 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32521] VGAM849 gene encodes a VGAM849 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM849 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM849 precursor RNA is designated SEQ ID:835, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:835 is located at position 12797 relative to the genome of Lymphocystis Disease Virus 1.

[32522] VGAM849 precursor RNA folds onto itself, forming VGAM849 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[32523] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM849 folded precursor RNA into VGAM849 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM849 RNA is designated SEQ ID:3560, and  
is provided hereinbelow with reference to the sequence  
listing part.

[32524] VGAM849 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM849 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM849 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32525] VGAM849 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM849 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM849 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM849 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM849 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32526] The complementary binding of VGAM849 RNA, herein designated VGAM RNA, to host target binding sites on VGAM849 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM849 host target RNA into VGAM849 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32527] It is appreciated that VGAM849 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM849 host target genes. The mRNA of each one of this plurality of VGAM849 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM849 RNA, herein designated VGAM RNA, and which when bound by VGAM849 RNA causes inhibition of translation of respective one or more VGAM849 host target proteins.

[32528] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM849 gene, herein designated VGAM GENE, on one or more VGAM849 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32529] It is yet further appreciated that a function of VGAM849 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of viral infection by Lymphocystis Disease Virus 1. Specific functions, and accordingly utilities, of VGAM849 correlate with, and may be deduced from, the identity of the host target genes which VGAM849 binds and inhibits, and the function of these host target genes,

as elaborated hereinbelow.

[32530] Nucleotide sequences of the VGAM849 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM849 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM849 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM849 are further described hereinbelow with reference to Table 1.

[32531] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM849 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM849 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32532] As mentioned hereinabove with reference to Fig. 1, a function of VGAM849 gene, herein designated VGAM is inhibition of expression of VGAM849 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM849 correlate with, and may be deduced from, the identity of the target genes which VGAM849 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.



[32533] Heterogeneous Nuclear Ribonucleoprotein D-like (HNRPDL, Accession NM\_005463) is a VGAM849 host target gene. HNRPDL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HNRPDL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HNRPDL BINDING SITE, designated SEQ ID:11946, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32534] A function of VGAM849 is therefore inhibition of Heterogeneous Nuclear Ribonucleoprotein D-like (HNRPDL, Accession NM\_005463), a gene which binds to rna molecules that contain au-rich elements. Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HNRPDL. The function of HNRPDL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM144. Isocitrate Dehydrogenase 3 (NAD+) Alpha (IDH3A, Accession NM\_005530) is another VGAM849 host target gene. IDH3A BINDING SITE is HOST TARGET binding

site found in the 3' untranslated region of mRNA encoded by IDH3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IDH3A BINDING SITE, designated SEQ ID:12050, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32535] Another function of VGAM849 is therefore inhibition of Isocitrate Dehydrogenase 3 (NAD<sup>+</sup>) Alpha (IDH3A, Accession NM\_005530), a gene which decarboxylates isocitrate into alpha-ketoglutarate in the TCA cycle. Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IDH3A. The function of IDH3A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM349. Insulin Receptor Substrate 1 (IRS1, Accession NM\_005544) is another VGAM849 host target gene. IRS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IRS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of IRS1 BINDING SITE, designated SEQ ID:12067, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32536] Another function of VGAM849 is therefore inhibition of Insulin Receptor Substrate 1 (IRS1, Accession NM\_005544), a gene which may mediate the control of various cellular processes by insulin. Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IRS1. The function of IRS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM281.PAG (Accession NM\_018440) is another VGAM849 host target gene. PAG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAG BINDING SITE, designated SEQ ID:20507, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also design-

nated SEQ ID:3560.

[32537] Another function of VGAM849 is therefore inhibition of PAG (Accession NM\_018440). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAG. Tumor Protein P63 (TP63, Accession NM\_003722) is another VGAM849 host target gene. TP63 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TP63, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TP63 BINDING SITE, designated SEQ ID:9813, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32538] Another function of VGAM849 is therefore inhibition of Tumor Protein P63 (TP63, Accession NM\_003722). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TP63. Ras Homolog Gene Family, Member E (ARHE, Accession NM\_005168) is another VGAM849 host target gene. ARHE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by ARHE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHE BINDING SITE, designated SEQ ID:11665, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32539] Another function of VGAM849 is therefore inhibition of Ras Homolog Gene Family, Member E (ARHE, Accession NM\_005168). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHE. Chemokine (C-C motif) Receptor 8 (CCR8, Accession NM\_005201) is another VGAM849 host target gene. CCR8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CCR8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CCR8 BINDING SITE, designated SEQ ID:11700, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32540] Another function of VGAM849 is therefore inhibition of

Chemokine (C-C motif) Receptor 8 (CCR8, Accession NM\_005201). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CCR8. FLJ10110 (Accession NM\_017998) is another VGAM849 host target gene. FLJ10110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10110 BINDING SITE, designated SEQ ID:19726, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32541] Another function of VGAM849 is therefore inhibition of FLJ10110 (Accession NM\_017998). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10110. FLJ10895 (Accession NM\_019084) is another VGAM849 host target gene. FLJ10895 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10895, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10895 BINDING SITE, designated SEQ ID:21156, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32542] Another function of VGAM849 is therefore inhibition of FLJ10895 (Accession NM\_019084). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10895. KIAA0419 (Accession NM\_014711) is another VGAM849 host target gene. KIAA0419 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0419, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0419 BINDING SITE, designated SEQ ID:16257, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32543] Another function of VGAM849 is therefore inhibition of KIAA0419 (Accession NM\_014711). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0419. KIAA0445 (Accession NM\_014675) is another VGAM849 host target gene. KIAA0445 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0445, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0445 BINDING SITE, designated SEQ ID:16144, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32544] Another function of VGAM849 is therefore inhibition of KIAA0445 (Accession NM\_014675). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0445. KIAA1627 (Accession XM\_087571) is another VGAM849 host target gene. KIAA1627 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1627, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1627 BINDING SITE, designated SEQ ID:39343, to the nucleotide sequence of VGAM849 RNA, herein designated



VGAM RNA, also designated SEQ ID:3560.

[32545] Another function of VGAM849 is therefore inhibition of KIAA1627 (Accession XM\_087571). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1627. Mitogen-activated Protein Kinase Kinase 6 (MAP2K6, Accession NM\_031988) is another VGAM849 host target gene. MAP2K6 BINDING SITE1 and MAP2K6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MAP2K6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP2K6 BINDING SITE1 and MAP2K6 BINDING SITE2, designated SEQ ID:25699 and SEQ ID:8639 respectively, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32546] Another function of VGAM849 is therefore inhibition of Mitogen-activated Protein Kinase Kinase 6 (MAP2K6, Accession NM\_031988). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP2K6. LOC128338 (Accession XM\_059238) is another VGAM849

host target gene. LOC128338 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC128338, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC128338 BINDING SITE, designated SEQ ID:36924, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32547] Another function of VGAM849 is therefore inhibition of LOC128338 (Accession XM\_059238). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC128338. LOC130507 (Accession XM\_059440) is another VGAM849 host target gene. LOC130507 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130507, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130507 BINDING SITE, designated SEQ ID:36994, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32548] Another function of VGAM849 is therefore inhibition of LOC130507 (Accession XM\_059440). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130507. LOC137090 (Accession XM\_070226) is another VGAM849 host target gene. LOC137090 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC137090, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC137090 BINDING SITE, designated SEQ ID:37392, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32549] Another function of VGAM849 is therefore inhibition of LOC137090 (Accession XM\_070226). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC137090. LOC144262 (Accession XM\_084793) is another VGAM849 host target gene. LOC144262 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC144262, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144262 BINDING SITE, designated SEQ ID:37702, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32550] Another function of VGAM849 is therefore inhibition of LOC144262 (Accession XM\_084793). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144262. LOC145482 (Accession XM\_085154) is another VGAM849 host target gene. LOC145482 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145482, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145482 BINDING SITE, designated SEQ ID:37876, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32551] Another function of VGAM849 is therefore inhibition of LOC145482 (Accession XM\_085154). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC145482. LOC149579 (Accession XM\_048743) is another VGAM849 host target gene. LOC149579 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149579, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149579 BINDING SITE, designated SEQ ID:35240, to the nucleotide sequence of VGAM849 RNA, herein designated VGAM RNA, also designated SEQ ID:3560.

[32552] Another function of VGAM849 is therefore inhibition of LOC149579 (Accession XM\_048743). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149579. LOC154792 (Accession XM\_098608) is another VGAM849 host target gene. LOC154792 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC154792, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC154792 BINDING SITE, designated SEQ ID:41727, to the nucleotide sequence of VGAM849 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3560.

[32553] Another function of VGAM849 is therefore inhibition of LOC154792 (Accession XM\_098608). Accordingly, utilities of VGAM849 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC154792. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 850 (VGAM850) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32554] VGAM850 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM850 was detected is described hereinabove with reference to Figs. 1–8.

[32555] VGAM850 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM850 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32556] VGAM850 gene encodes a VGAM850 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM850 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM850 precursor RNA is designated SEQ ID:836, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:836 is located at position 13536 relative to the genome of Lymphocystis Disease Virus 1.

[32557] VGAM850 precursor RNA folds onto itself, forming VGAM850 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32558] An enzyme complex designated DICER COMPLEX, `dices` the VGAM850 folded precursor RNA into VGAM850 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM850 RNA is designated SEQ ID:3561, and is provided hereinbelow with reference to the sequence listing part.

[32559] VGAM850 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM850 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM850 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[32560] VGAM850 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM850 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM850 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and



BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM850 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM850 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32561] The complementary binding of VGAM850 RNA, herein designated VGAM RNA, to host target binding sites on VGAM850 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM850 host target RNA into VGAM850 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32562] It is appreciated that VGAM850 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM850 host target genes. The mRNA of

each one of this plurality of VGAM850 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM850 RNA, herein designated VGAM RNA, and which when bound by VGAM850 RNA causes inhibition of translation of respective one or more VGAM850 host target proteins.

[32563] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM850 gene, herein designated VGAM GENE, on one or more VGAM850 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[32564] It is yet further appreciated that a function of VGAM850 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of viral infection by Lymphocystis Disease Virus 1. Specific functions, and accordingly utilities, of VGAM850 correlate with, and may be deduced from, the identity of the host target genes which VGAM850 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32565] Nucleotide sequences of the VGAM850 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM850 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM850 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM850 are further described hereinbelow with reference to Table 1.

[32566] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM850 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM850 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[32567] As mentioned hereinabove with reference to Fig. 1, a function of VGAM850 gene, herein designated VGAM is inhibition of expression of VGAM850 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM850 correlate with, and may be deduced from, the identity of the target genes which VGAM850 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32568] Actinin, Alpha 2 (ACTN2, Accession NM\_001103) is a VGAM850 host target gene. ACTN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ACTN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACTN2 BINDING SITE, designated SEQ ID:6758, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32569] A function of VGAM850 is therefore inhibition of Actinin, Alpha 2 (ACTN2, Accession NM\_001103), a gene which an actin-binding protein with multiple roles in different cell

types. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACTN2. The function of ACTN2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM88.UDP-Gal:betaGlcNAc Beta 1,4- Galactosyltransferase, Polypeptide 1 (B4GALT1, Accession NM\_001497) is another VGAM850 host target gene. B4GALT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by B4GALT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of B4GALT1 BINDING SITE, designated SEQ ID:7247, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32570] Another function of VGAM850 is therefore inhibition of UDP-Gal:betaGlcNAc Beta 1,4- Galactosyltransferase, Polypeptide 1 (B4GALT1, Accession NM\_001497). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with B4GALT1. Bromodomain and PHD Finger Con-

taining, 1 (BRPF1, Accession XM\_054520) is another VGAM850 host target gene. BRPF1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BRPF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BRPF1 BINDING SITE, designated SEQ ID:36174, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32571] Another function of VGAM850 is therefore inhibition of Bromodomain and PHD Finger Containing, 1 (BRPF1, Accession XM\_054520), a gene which has 6 zinc finger motifs and a bromodomain. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BRPF1. The function of BRPF1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM497. Carcinoembryonic Antigen-related Cell Adhesion Molecule 6 (non-specific cross reacting antigen) (CEACAM6, Accession NM\_002483) is another VGAM850 host target gene. CEACAM6 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by CEACAM6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CEACAM6 BINDING SITE, designated SEQ ID:8310, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32572] Another function of VGAM850 is therefore inhibition of Carcinoembryonic Antigen-related Cell Adhesion Molecule 6 (non-specific cross reacting antigen) (CEACAM6, Accession NM\_002483), a gene which Non-specific cross reacting antigen (. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CEACAM6. The function of CEACAM6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM286. Cartilage Associated Protein (CRTAP, Accession NM\_006371) is another VGAM850 host target gene. CRTAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRTAP, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRTAP BINDING SITE, designated SEQ ID:13062, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32573] Another function of VGAM850 is therefore inhibition of Cartilage Associated Protein (CRTAP, Accession NM\_006371), a gene which is a novel developmentally regulated chick embryo protein. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRTAP. The function of CRTAP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM152. Dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2) (DPP4, Accession NM\_001935) is another VGAM850 host target gene. DPP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DPP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of



DPP4 BINDING SITE, designated SEQ ID:7648, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32574] Another function of VGAM850 is therefore inhibition of Dipeptidylpeptidase IV (CD26, adenosine deaminase complexing protein 2) (DPP4, Accession NM\_001935), a gene which removes n-terminal dipeptides sequentially from polypeptides. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DPP4. The function of DPP4 has been established by previous studies. Koch and Shows (1979, 1980) concluded that at least 3 genes are involved in the expression of adenosine deaminase complexing protein: ADA (OMIM Ref. No. 102700) on chromosome 20, ADCP1 (OMIM Ref. No. 102710) on chromosome 6, and ADCP2 on chromosome 2. On the other hand, from studies in mouse-man and hamster-man hybrid cells, Herschleb-Voogt et al. (1981) concluded that a gene or genes on human chromosome 2 determine the expression of ADCP and that neither chromosome 6 nor any other of the chromosomes of man carries genes involved in the formation of ADCP. Van Cong et al. (1981) concluded that the gene for ADCP on chromosome 2 is located between

MDH1 (OMIM Ref. No. 154200) and IDH1 (OMIM Ref. No. 147700), i.e., in the segment 2p23–q32. Could one form of adenosine deaminase deficiency (leading to severe combined immunodeficiency) represent, in fact, deficiency of the complexing protein? Dipeptidyl peptidase IV (DPP4; EC 3.4.14.5) is identical to ADA complexing protein–2 and to the T–cell activation antigen CD26. DPP4 is a serine exopeptidase that cleaves X–proline dipeptides from the N terminus of polypeptides. It is an intrinsic membrane glycoprotein anchored into the cell membrane by its N–terminal end. High levels of the enzyme are found in the brush–border membranes of the kidney proximal tubule and of the small intestine, but several other tissues also express the enzyme. The enzyme is present in the fetal colon but disappears at birth. It is ectopically expressed in some human colon adenocarcinomas and human colon cancer cell lines. From such a colon cancer cell line, Darmoul et al. (1990) isolated a cDNA probe for intestinal dipeptidyl peptidase IV and, by Southern analysis of somatic cell hybrids, assigned the gene to chromosome 2. This assignment was confirmed by Mathew et al. (1994), who sublocalized the DPP4 gene to 2q23 by fluorescence in situ hybridization. Misumi et al. (1992) isolated and se–

quenced the cDNA coding for DPP4. The nucleotide sequence (3,465 bp) of the cDNA contained an open reading frame encoding a polypeptide comprising 766 amino acids, 1 residue less than those of the rat protein. The predicted amino acid sequence exhibited 84.9% identity to that of the rat enzyme.

[32575] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32576] Mathew, S.; Morrison, M. E.; Murty, V. V. V. S.; Houghton, A. N.; Chaganti, R. S. K. : Assignment of the DPP4 gene encoding adenosine deaminase binding protein (CD26/dipeptidylpeptidase IV) to 2q23. *Genomics* 22: 211–212, 1994. ; and

[32577] Van Cong, N.; Weil, D.; Gross, M.–S.; Foubert, C.; Jami, J.; Frezal, J. : Controle genetique et epigenetique de l'expression de l'adenosine deaminase. *Analyse des cellules humaines et h.*

[32578] Further studies establishing the function and utilities of DPP4 are found in John Hopkins OMIM database record ID 102720, and in cited publications numbered 2347–235 and 12114–2357 listed in the bibliography section hereinbelow, which are also hereby incorporated by refer–

ence.Follistatin-like 1 (FSTL1, Accession NM\_007085) is another VGAM850 host target gene. FSTL1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FSTL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FSTL1 BINDING SITE, designated SEQ ID:13952, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32579] Another function of VGAM850 is therefore inhibition of Follistatin-like 1 (FSTL1, Accession NM\_007085), a gene which may modulate the action of some growth factors on cell proliferation and differentiation. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FSTL1. The function of FSTL1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM791.Fucosyltransferase 9 (alpha (1,3) Fucosyltransferase) (FUT9, Accession XM\_042167) is another VGAM850 host target gene. FUT9 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by FUT9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FUT9 BINDING SITE, designated SEQ ID:33701, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32580] Another function of VGAM850 is therefore inhibition of Fucosyltransferase 9 (alpha (1,3) Fucosyltransferase) (FUT9, Accession XM\_042167), a gene which catalyzes alpha-1,3 glycosidic linkages. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FUT9. The function of FUT9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM206. GM2 Ganglioside Activator Protein (GM2A, Accession XM\_041978) is another VGAM850 host target gene. GM2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GM2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of GM2A BINDING SITE, designated SEQ ID:33660, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32581] Another function of VGAM850 is therefore inhibition of GM2 Ganglioside Activator Protein (GM2A, Accession XM\_041978). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GM2A. Nucleoporin 62kDa (NUP62, Accession NM\_016553) is another VGAM850 host target gene. NUP62 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUP62, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUP62 BINDING SITE, designated SEQ ID:18629, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32582] Another function of VGAM850 is therefore inhibition of Nucleoporin 62kDa (NUP62, Accession NM\_016553). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with NUP62. Pleiomorphic Adenoma Gene 1 (PLAG1, Accession NM\_002655) is another VGAM850 host target gene. PLAG1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PLAG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLAG1 BINDING SITE, designated SEQ ID:8522, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32583] Another function of VGAM850 is therefore inhibition of Pleiomorphic Adenoma Gene 1 (PLAG1, Accession NM\_002655), a gene which contains a zinc finger domain. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLAG1. The function of PLAG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM29. Plexin A2 (PLXNA2, Accession NM\_025179) is another VGAM850 host target gene. PLXNA2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by

PLXNA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLXNA2 BINDING SITE, designated SEQ ID:24815, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32584] Another function of VGAM850 is therefore inhibition of Plexin A2 (PLXNA2, Accession NM\_025179), a gene which is a transmembrane protein. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLXNA2. The function of PLXNA2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM538. Protein Phosphatase 2, Regulatory Subunit B (B56), Beta Isoform (PPP2R5B, Accession NM\_006244) is another VGAM850 host target gene. PPP2R5B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP2R5B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of



PPP2R5B BINDING SITE, designated SEQ ID:12914, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32585] Another function of VGAM850 is therefore inhibition of Protein Phosphatase 2, Regulatory Subunit B (B56), Beta Isoform (PPP2R5B, Accession NM\_006244), a gene which is a regulatory subunit of protein phosphatase 2A. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R5B. The function of PPP2R5B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM264. Transformation/transcription Domain-associated Protein (TRRAP, Accession NM\_003496) is another VGAM850 host target gene. TRRAP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRRAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRRAP BINDING SITE, designated SEQ ID:9590, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3561.

[32586] Another function of VGAM850 is therefore inhibition of Transformation/transcription Domain-associated Protein (TRRAP, Accession NM\_003496). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRRAP. Vitronectin (serum spreading factor, somatomedin B, complement S-protein) (VTN, Accession NM\_000638) is another VGAM850 host target gene. VTN BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by VTN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VTN BINDING SITE, designated SEQ ID:6273, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32587] Another function of VGAM850 is therefore inhibition of Vitronectin (serum spreading factor, somatomedin B, complement S-protein) (VTN, Accession NM\_000638), a gene which is a cell adhesion and spreading factor found in serum and tissues. Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with VTN. The function of VTN has been established by previous studies. Vitronectin, also called serum spreading factor or complement S-protein, is a 75-kD glycoprotein in plasma and tissue. (S-protein is not to be confused with protein S (OMIM Ref. No. 176880).) A multifunctional protein, it promotes attachment and spreading of animal cells in vitro, inhibits cytolysis by the complement C5b-9 complex, and modulates antithrombin III-thrombin action in blood coagulation. The primary structure of vitronectin has been deduced from the sequence of its cloned cDNA (Jenne and Stanley, 1985; Preissner et al., 1986). Polymorphism of vitronectin of plasma has been demonstrated (Conlon et al., 1988; Kubota et al., 1988). Sun and Mosher (1989) demonstrated that the frequencies are different in Orientals and Caucasians. By use of high resolution fluorescence in situ hybridization (FISH), Fink et al. (1992) mapped the VTN gene to 17q11. The localization was confirmed by cohybridization with a centromere-specific alphoid probe.

[32588] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [32589] Kubota, K.; Katayama, S.; Matsuda, M.; Hayashi, M. : Three types of vitronectin in human blood. Cell Struct. Funct. 13: 123–128, 1988. ; and
- [32590] Sun, W. H.; Mosher, D. F. : Polymorphism of vitronectin. (Letter) Blood 73: 353–354, 1989.
- [32591] Further studies establishing the function and utilities of VTN are found in John Hopkins OMIM database record ID 193190, and in cited publications numbered 14–19 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 22 Open Reading Frame 5 (C22orf5, Accession NM\_012264) is another VGAM850 host target gene. C22orf5 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by C22orf5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C22orf5 BINDING SITE, designated SEQ ID:14584, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.
- [32592] Another function of VGAM850 is therefore inhibition of Chromosome 22 Open Reading Frame 5 (C22orf5, Accession NM\_012264). Accordingly, utilities of VGAM850 in–

clude diagnosis, prevention and treatment of diseases and clinical conditions associated with C22orf5. Caspase Recruitment Domain Family, Member 14 (CARD14, Accession NM\_024110) is another VGAM850 host target gene.

CARD14 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CARD14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CARD14 BINDING SITE, designated SEQ ID:23557, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32593] Another function of VGAM850 is therefore inhibition of Caspase Recruitment Domain Family, Member 14 (CARD14, Accession NM\_024110). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CARD14. Carcinoembryonic Antigen-related Cell Adhesion Molecule 7 (CEACAM7, Accession NM\_006890) is another VGAM850 host target gene. CEACAM7 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CEACAM7, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CEACAM7 BINDING SITE, designated SEQ ID:13757, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32594] Another function of VGAM850 is therefore inhibition of Carcinoembryonic Antigen-related Cell Adhesion Molecule 7 (CEACAM7, Accession NM\_006890). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CEACAM7. Centaurin, Gamma 2 (CENTG2, Accession NM\_014914) is another VGAM850 host target gene. CENTG2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CENTG2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CENTG2 BINDING SITE, designated SEQ ID:17159, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32595] Another function of VGAM850 is therefore inhibition of

Centaurin, Gamma 2 (CENTG2, Accession NM\_014914). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CENTG2. CUG Triplet Repeat, RNA Binding Protein 2 (CUGBP2, Accession NM\_006561) is another VGAM850 host target gene. CUGBP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CUGBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CUGBP2 BINDING SITE, designated SEQ ID:13331, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32596] Another function of VGAM850 is therefore inhibition of CUG Triplet Repeat, RNA Binding Protein 2 (CUGBP2, Accession NM\_006561). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CUGBP2. CXYorf1 (Accession XM\_088704) is another VGAM850 host target gene. CXYorf1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CXYorf1, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CXYorf1 BINDING SITE, designated SEQ ID:39909, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32597] Another function of VGAM850 is therefore inhibition of CXYorf1 (Accession XM\_088704). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CXYorf1. FLJ10716 (Accession NM\_018191) is another VGAM850 host target gene. FLJ10716 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10716, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10716 BINDING SITE, designated SEQ ID:20047, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32598] Another function of VGAM850 is therefore inhibition of FLJ10716 (Accession NM\_018191). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with FLJ10716. FLJ10719 (Accession XM\_031328) is another VGAM850 host target gene. FLJ10719 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10719, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10719 BINDING SITE, designated SEQ ID:31340, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32599] Another function of VGAM850 is therefore inhibition of FLJ10719 (Accession XM\_031328). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10719. FLJ20296 (Accession NM\_017750) is another VGAM850 host target gene. FLJ20296 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20296, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20296 BINDING SITE, designated SEQ ID:19355, to the nucleotide sequence of

VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32600] Another function of VGAM850 is therefore inhibition of FLJ20296 (Accession NM\_017750). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20296. FLJ20772 (Accession NM\_017956) is another VGAM850 host target gene. FLJ20772 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20772, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20772 BINDING SITE, designated SEQ ID:19666, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32601] Another function of VGAM850 is therefore inhibition of FLJ20772 (Accession NM\_017956). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20772. FLJ22215 (Accession XM\_173021) is another VGAM850 host target gene. FLJ22215 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ22215, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22215 BINDING SITE, designated SEQ ID:46282, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32602] Another function of VGAM850 is therefore inhibition of FLJ22215 (Accession XM\_173021). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22215. FLJ32752 (Accession NM\_144666) is another VGAM850 host target gene. FLJ32752 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ32752, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32752 BINDING SITE, designated SEQ ID:29482, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32603] Another function of VGAM850 is therefore inhibition of FLJ32752 (Accession NM\_144666). Accordingly, utilities of

VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32752. GRB2-associated Binding Protein 3 (GAB3, Accession NM\_080612) is another VGAM850 host target gene. GAB3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAB3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAB3 BINDING SITE, designated SEQ ID:27928, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32604] Another function of VGAM850 is therefore inhibition of GRB2-associated Binding Protein 3 (GAB3, Accession NM\_080612). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAB3. GR6 (Accession NM\_007354) is another VGAM850 host target gene. GR6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GR6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

GR6 BINDING SITE, designated SEQ ID:14284, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32605] Another function of VGAM850 is therefore inhibition of GR6 (Accession NM\_007354). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GR6. HSPC213 (Accession NM\_016475) is another VGAM850 host target gene. HSPC213 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPC213, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC213 BINDING SITE, designated SEQ ID:18576, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32606] Another function of VGAM850 is therefore inhibition of HSPC213 (Accession NM\_016475). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC213. Interleukin 17D (IL17D, Accession NM\_138284) is another VGAM850 host target gene. IL17D BINDING SITE is HOST

TARGET binding site found in the 3' untranslated region of mRNA encoded by IL17D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL17D BINDING SITE, designated SEQ ID:28700, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32607] Another function of VGAM850 is therefore inhibition of Interleukin 17D (IL17D, Accession NM\_138284). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL17D. KH Domain Containing, RNA Binding, Signal Transduction Associated 1 (KHDRBS1, Accession NM\_006559) is another VGAM850 host target gene. KHDRBS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KHDRBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KHDRBS1 BINDING SITE, designated SEQ ID:13328, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ

ID:3561.

[32608] Another function of VGAM850 is therefore inhibition of KH Domain Containing, RNA Binding, Signal Transduction Associated 1 (KHDRBS1, Accession NM\_006559). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KHDRBS1. KIAA0298 (Accession XM\_084529) is another VGAM850 host target gene. KIAA0298 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0298, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0298 BINDING SITE, designated SEQ ID:37627, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32609] Another function of VGAM850 is therefore inhibition of KIAA0298 (Accession XM\_084529). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0298. KIAA0461 (Accession XM\_047883) is another VGAM850 host target gene. KIAA0461 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA0461, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0461 BINDING SITE, designated SEQ ID:35075, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32610] Another function of VGAM850 is therefore inhibition of KIAA0461 (Accession XM\_047883). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0461. KIAA0493 (Accession XM\_034717) is another VGAM850 host target gene. KIAA0493 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0493, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0493 BINDING SITE, designated SEQ ID:32142, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32611] Another function of VGAM850 is therefore inhibition of KIAA0493 (Accession XM\_034717). Accordingly, utilities



of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0493. KIAA0766 (Accession NM\_014805) is another VGAM850 host target gene. KIAA0766 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0766, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0766 BINDING SITE, designated SEQ ID:16743, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32612] Another function of VGAM850 is therefore inhibition of KIAA0766 (Accession NM\_014805). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0766. KIAA0853 (Accession NM\_015070) is another VGAM850 host target gene. KIAA0853 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0853, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA0853 BINDING SITE, designated SEQ ID:17437, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32613] Another function of VGAM850 is therefore inhibition of KIAA0853 (Accession NM\_015070). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0853. KIAA0978 (Accession XM\_047013) is another VGAM850 host target gene. KIAA0978 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0978, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0978 BINDING SITE, designated SEQ ID:34887, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32614] Another function of VGAM850 is therefore inhibition of KIAA0978 (Accession XM\_047013). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0978. KIAA1530 (Accession XM\_042661) is another VGAM850 host target gene. KIAA1530 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1530, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1530 BINDING SITE, designated SEQ ID:33735, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32615] Another function of VGAM850 is therefore inhibition of KIAA1530 (Accession XM\_042661). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1530. KIAA1559 (Accession XM\_054472) is another VGAM850 host target gene. KIAA1559 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1559, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1559 BINDING SITE, designated SEQ ID:36164, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32616] Another function of VGAM850 is therefore inhibition of

KIAA1559 (Accession XM\_054472). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1559. MGC2835 (Accession NM\_024072) is another VGAM850 host target gene. MGC2835 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2835, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2835 BINDING SITE, designated SEQ ID:23506, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32617] Another function of VGAM850 is therefore inhibition of MGC2835 (Accession NM\_024072). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2835. MGC2865 (Accession NM\_032375) is another VGAM850 host target gene. MGC2865 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC2865, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of MGC2865 BINDING SITE, designated SEQ ID:26168, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32618] Another function of VGAM850 is therefore inhibition of MGC2865 (Accession NM\_032375). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2865. MGC3130 (Accession NM\_024032) is another VGAM850 host target gene. MGC3130 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC3130, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC3130 BINDING SITE, designated SEQ ID:23461, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32619] Another function of VGAM850 is therefore inhibition of MGC3130 (Accession NM\_024032). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC3130. moblak (Accession NM\_130807) is another

VGAM850 host target gene. moblak BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by moblak, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of moblak BINDING SITE, designated SEQ ID:28309, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32620] Another function of VGAM850 is therefore inhibition of moblak (Accession NM\_130807). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with moblak. Myozenin 2 (MYOZ2, Accession NM\_016599) is another VGAM850 host target gene. MYOZ2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYOZ2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYOZ2 BINDING SITE, designated SEQ ID:18692, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32621] Another function of VGAM850 is therefore inhibition of Myozenin 2 (MYOZ2, Accession NM\_016599). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYOZ2. NDP52 (Accession NM\_005831) is another VGAM850 host target gene. NDP52 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NDP52, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDP52 BINDING SITE, designated SEQ ID:12444, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32622] Another function of VGAM850 is therefore inhibition of NDP52 (Accession NM\_005831). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDP52. Nei Like 2 (E. coli) (NEIL2, Accession NM\_145043) is another VGAM850 host target gene. NEIL2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NEIL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEIL2 BINDING SITE, designated SEQ ID:29675, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32623] Another function of VGAM850 is therefore inhibition of Nei Like 2 (E. coli) (NEIL2, Accession NM\_145043). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEIL2. NRF (Accession NM\_017544) is another VGAM850 host target gene. NRF BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NRF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRF BINDING SITE, designated SEQ ID:18988, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.



[32624] Another function of VGAM850 is therefore inhibition of NRF (Accession NM\_017544). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRF. Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230) is another VGAM850 host target gene. NUDT11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUDT11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUDT11 BINDING SITE, designated SEQ ID:30144, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32625] Another function of VGAM850 is therefore inhibition of Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUDT11. Protein Kinase C and Casein Kinase Substrate In Neurons 2 (PACSIN2, Accession NM\_007229) is another VGAM850 host target gene. PACSIN2 BINDING SITE is

HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PACSIN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PACSIN2 BINDING SITE, designated SEQ ID:14097, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32626] Another function of VGAM850 is therefore inhibition of Protein Kinase C and Casein Kinase Substrate In Neurons 2 (PACSIN2, Accession NM\_007229). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PACSIN2. Protein Phosphatase 1, Regulatory Subunit 10 (PPP1R10, Accession NM\_002714) is another VGAM850 host target gene. PPP1R10 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PPP1R10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R10 BINDING SITE, designated SEQ ID:8577, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ

ID:3561.

[32627] Another function of VGAM850 is therefore inhibition of Protein Phosphatase 1, Regulatory Subunit 10 (PPP1R10, Accession NM\_002714). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R10. RBT1 (Accession NM\_013368) is another VGAM850 host target gene. RBT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RBT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RBT1 BINDING SITE, designated SEQ ID:15011, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32628] Another function of VGAM850 is therefore inhibition of RBT1 (Accession NM\_013368). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RBT1. Solute Carrier Family 39 (zinc transporter), Member 3 (SLC39A3, Accession NM\_144564) is another VGAM850 host target gene. SLC39A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by SLC39A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC39A3 BINDING SITE, designated SEQ ID:29359, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32629] Another function of VGAM850 is therefore inhibition of Solute Carrier Family 39 (zinc transporter), Member 3 (SLC39A3, Accession NM\_144564). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC39A3. SV2 (Accession NM\_014849) is another VGAM850 host target gene. SV2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SV2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SV2 BINDING SITE, designated SEQ ID:16885, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32630] Another function of VGAM850 is therefore inhibition of SV2 (Accession NM\_014849). Accordingly, utilities of

VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SV2.

TAF9-like RNA Polymerase II, TATA Box Binding Protein (TBP)-associated Factor, 31kDa (TAF9L, Accession NM\_015975) is another VGAM850 host target gene. TAF9L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TAF9L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAF9L BINDING SITE, designated SEQ ID:18075, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32631] Another function of VGAM850 is therefore inhibition of TAF9-like RNA Polymerase II, TATA Box Binding Protein (TBP)-associated Factor, 31kDa (TAF9L, Accession NM\_015975). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAF9L. TUBB5 (Accession NM\_006087) is another VGAM850 host target gene. TUBB5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TUBB5, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TUBB5 BINDING SITE, designated SEQ ID:12730, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32632] Another function of VGAM850 is therefore inhibition of TUBB5 (Accession NM\_006087). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TUBB5. Upstream Binding Protein 1 (LBP-1a) (UBP1, Accession NM\_014517) is another VGAM850 host target gene. UB1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UB1 BINDING SITE, designated SEQ ID:15847, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32633] Another function of VGAM850 is therefore inhibition of Upstream Binding Protein 1 (LBP-1a) (UBP1, Accession NM\_014517). Accordingly, utilities of VGAM850 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with UBP1. LOC125456 (Accession XM\_064620) is another VGAM850 host target gene. LOC125456 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC125456, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC125456 BINDING SITE, designated SEQ ID:37266, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32634] Another function of VGAM850 is therefore inhibition of LOC125456 (Accession XM\_064620). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125456. LOC125929 (Accession XM\_064872) is another VGAM850 host target gene. LOC125929 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC125929, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC125929 BINDING SITE, designated SEQ ID:37269, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32635] Another function of VGAM850 is therefore inhibition of LOC125929 (Accession XM\_064872). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125929. LOC144438 (Accession XM\_084860) is another VGAM850 host target gene. LOC144438 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144438, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144438 BINDING SITE, designated SEQ ID:37738, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32636] Another function of VGAM850 is therefore inhibition of LOC144438 (Accession XM\_084860). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144438. LOC146733 (Accession XM\_097076) is another VGAM850 host target gene. LOC146733 BINDING



SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC146733, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146733 BINDING SITE, designated SEQ ID:40730, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32637] Another function of VGAM850 is therefore inhibition of LOC146733 (Accession XM\_097076). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146733. LOC149668 (Accession XM\_097692) is another VGAM850 host target gene. LOC149668 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC149668, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149668 BINDING SITE, designated SEQ ID:41030, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32638] Another function of VGAM850 is therefore inhibition of

LOC149668 (Accession XM\_097692). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149668. LOC149911 (Accession XM\_097735) is another VGAM850 host target gene. LOC149911 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149911, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149911 BINDING SITE, designated SEQ ID:41083, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32639] Another function of VGAM850 is therefore inhibition of LOC149911 (Accession XM\_097735). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149911. LOC150271 (Accession XM\_097859) is another VGAM850 host target gene. LOC150271 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150271, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC150271 BINDING SITE, designated SEQ ID:41172, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32640] Another function of VGAM850 is therefore inhibition of LOC150271 (Accession XM\_097859). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150271. LOC151647 (Accession XM\_087261) is another VGAM850 host target gene. LOC151647 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151647, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151647 BINDING SITE, designated SEQ ID:39155, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32641] Another function of VGAM850 is therefore inhibition of LOC151647 (Accession XM\_087261). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151647. LOC152220 (Accession XM\_098176) is an-

other VGAM850 host target gene. LOC152220 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152220, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152220 BINDING SITE, designated SEQ ID:41444, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32642] Another function of VGAM850 is therefore inhibition of LOC152220 (Accession XM\_098176). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152220. LOC155054 (Accession XM\_088140) is another VGAM850 host target gene. LOC155054 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC155054, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC155054 BINDING SITE, designated SEQ ID:39540, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32643] Another function of VGAM850 is therefore inhibition of LOC155054 (Accession XM\_088140). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC155054. LOC158055 (Accession XM\_088453) is another VGAM850 host target gene. LOC158055 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158055, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158055 BINDING SITE, designated SEQ ID:39706, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32644] Another function of VGAM850 is therefore inhibition of LOC158055 (Accession XM\_088453). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158055. LOC200093 (Accession XM\_032184) is another VGAM850 host target gene. LOC200093 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200093, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200093 BINDING SITE, designated SEQ ID:31601, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32645] Another function of VGAM850 is therefore inhibition of LOC200093 (Accession XM\_032184). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200093. LOC200310 (Accession XM\_037840) is another VGAM850 host target gene. LOC200310 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200310, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200310 BINDING SITE, designated SEQ ID:32709, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32646] Another function of VGAM850 is therefore inhibition of LOC200310 (Accession XM\_037840). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC200310. LOC202024 (Accession XM\_114422) is another VGAM850 host target gene. LOC202024 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202024, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202024 BINDING SITE, designated SEQ ID:42959, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32647] Another function of VGAM850 is therefore inhibition of LOC202024 (Accession XM\_114422). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202024. LOC202347 (Accession XM\_117390) is another VGAM850 host target gene. LOC202347 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202347, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202347 BINDING SITE, designated SEQ ID:43431, to the nucleotide sequence of VGAM850 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3561.

[32648] Another function of VGAM850 is therefore inhibition of LOC202347 (Accession XM\_117390). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202347. LOC202934 (Accession XM\_117486) is another VGAM850 host target gene. LOC202934 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202934, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202934 BINDING SITE, designated SEQ ID:43461, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32649] Another function of VGAM850 is therefore inhibition of LOC202934 (Accession XM\_117486). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202934. LOC220514 (Accession XM\_017498) is another VGAM850 host target gene. LOC220514 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220514, cor-



responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220514 BINDING SITE, designated SEQ ID:30321, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32650] Another function of VGAM850 is therefore inhibition of LOC220514 (Accession XM\_017498). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220514. LOC220776 (Accession XM\_043388) is another VGAM850 host target gene. LOC220776 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220776, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220776 BINDING SITE, designated SEQ ID:33935, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32651] Another function of VGAM850 is therefore inhibition of LOC220776 (Accession XM\_043388). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC220776. LOC221931 (Accession XM\_168348) is another VGAM850 host target gene. LOC221931 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC221931, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221931 BINDING SITE, designated SEQ ID:45119, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32652] Another function of VGAM850 is therefore inhibition of LOC221931 (Accession XM\_168348). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221931. LOC253675 (Accession XM\_172990) is another VGAM850 host target gene. LOC253675 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC253675, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253675 BINDING SITE, designated SEQ ID:46265, to

the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32653] Another function of VGAM850 is therefore inhibition of LOC253675 (Accession XM\_172990). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253675. LOC253782 (Accession XM\_171023) is another VGAM850 host target gene. LOC253782 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253782, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253782 BINDING SITE, designated SEQ ID:45798, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32654] Another function of VGAM850 is therefore inhibition of LOC253782 (Accession XM\_171023). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253782. LOC254428 (Accession XM\_170932) is another VGAM850 host target gene. LOC254428 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC254428, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254428 BINDING SITE, designated SEQ ID:45718, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32655] Another function of VGAM850 is therefore inhibition of LOC254428 (Accession XM\_170932). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254428. LOC254848 (Accession XM\_173133) is another VGAM850 host target gene. LOC254848 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254848 BINDING SITE, designated SEQ ID:46381, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32656] Another function of VGAM850 is therefore inhibition of LOC254848 (Accession XM\_173133). Accordingly, utilities

of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254848. LOC56267 (Accession NM\_019610) is another VGAM850 host target gene. LOC56267 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC56267, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC56267 BINDING SITE, designated SEQ ID:21228, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32657] Another function of VGAM850 is therefore inhibition of LOC56267 (Accession NM\_019610). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC56267. LOC57105 (Accession NM\_020377) is another VGAM850 host target gene. LOC57105 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC57105, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC57105 BINDING SITE, designated SEQ ID:21641, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32658] Another function of VGAM850 is therefore inhibition of LOC57105 (Accession NM\_020377). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57105. LOC83693 (Accession NM\_031463) is another VGAM850 host target gene. LOC83693 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC83693, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC83693 BINDING SITE, designated SEQ ID:25496, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32659] Another function of VGAM850 is therefore inhibition of LOC83693 (Accession NM\_031463). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC83693. LOC90670 (Accession XM\_033352) is another VGAM850 host target gene. LOC90670 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90670, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90670 BINDING SITE, designated SEQ ID:31882, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32660] Another function of VGAM850 is therefore inhibition of LOC90670 (Accession XM\_033352). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90670. LOC91040 (Accession XM\_035641) is another VGAM850 host target gene. LOC91040 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91040 BINDING SITE, designated SEQ ID:32318, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32661] Another function of VGAM850 is therefore inhibition of

LOC91040 (Accession XM\_035641). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91040. LOC96597 (Accession XM\_039922) is another VGAM850 host target gene. LOC96597 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC96597, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC96597 BINDING SITE, designated SEQ ID:33232, to the nucleotide sequence of VGAM850 RNA, herein designated VGAM RNA, also designated SEQ ID:3561.

[32662] Another function of VGAM850 is therefore inhibition of LOC96597 (Accession XM\_039922). Accordingly, utilities of VGAM850 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC96597. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 851 (VGAM851) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is



known in the art.

[32663] VGAM851 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM851 was detected is described hereinabove with reference to Figs. 1–8.

[32664] VGAM851 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Lymphocystis Disease Virus 1. VGAM851 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32665] VGAM851 gene encodes a VGAM851 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM851 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM851 precursor RNA is designated SEQ ID:837, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:837 is located at position 13906 relative to the genome of Lymphocystis Disease Virus 1.

[32666] VGAM851 precursor RNA folds onto itself, forming VGAM851 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[32667] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM851 folded precursor RNA into VGAM851 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 41%) nucleotide se-  
quence of VGAM851 RNA is designated SEQ ID:3562, and  
is provided hereinbelow with reference to the sequence  
listing part.

[32668] VGAM851 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM851 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM851 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32669] VGAM851 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM851 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM851 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM851 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM851 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[32670] The complementary binding of VGAM851 RNA, herein designated VGAM RNA, to host target binding sites on VGAM851 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM851 host target RNA into VGAM851 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32671] It is appreciated that VGAM851 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM851 host target genes. The mRNA of each one of this plurality of VGAM851 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM851 RNA, herein designated VGAM RNA, and which when bound by VGAM851 RNA causes inhibition of translation of respective one or more VGAM851 host target proteins.

[32672] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM851 gene, herein designated VGAM GENE, on one or

more VGAM851 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32673] It is yet further appreciated that a function of VGAM851 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of viral infection by Lymphocystis Disease Virus 1. Specific functions, and accordingly utilities, of VGAM851 correlate with, and may be deduced from, the identity of the host target genes which VGAM851 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [32674] Nucleotide sequences of the VGAM851 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM851 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM851 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM851 are further described hereinbelow with reference to Table 1.
- [32675] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM851 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM851 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [32676] As mentioned hereinabove with reference to Fig. 1, a function of VGAM851 gene, herein designated VGAM is inhibition of expression of VGAM851 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM851 correlate with, and may be deduced from, the identity of the target genes which VGAM851 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [32677] Chloride Channel, Calcium Activated, Family Member 2

(CLCA2, Accession NM\_006536) is a VGAM851 host target gene. CLCA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLCA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLCA2 BINDING SITE, designated SEQ ID:13290, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32678] A function of VGAM851 is therefore inhibition of Chloride Channel, Calcium Activated, Family Member 2 (CLCA2, Accession NM\_006536), a gene which Calcium-sensitive chloride channel, is suggested to play a role in the complex pathogenesis of cystic fibrosis. Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLCA2. The function of CLCA2 has been established by previous studies. Members of the CLCA family of calcium-activated chloride channels, such as human CLCA1 (OMIM Ref. No. 603906) and bovine lung-endothelial cell adhesion molecule-1 (Lu-ECAM-1), appear to have a conserved structure and function but significantly different tissue

expression patterns. By screening a human lung cDNA library with a Lu-ECAM-1 cDNA, Gruber et al. (1999) isolated cDNAs encoding CLCA2. The 943-amino acid protein deduced from the CLCA2 cDNAs is 76% and 51% identical to Lu-ECAM-1 and human CLCA1, respectively. Glycosylation site scanning and protease protection assays predicted that CLCA2 has 5 transmembrane domains and a large N-terminal extracellular domain. CLCA2 also contains a signal sequence, conserved cysteine residues within its N-terminal extracellular domain, a conserved consensus site for monobasic proteolytic cleavage, several potential glycosylation sites, and a number of potential phosphorylation sites for protein kinase C (see OMIM Ref. No. 176982). Northern blot analysis detected a 3.6-kb CLCA2 transcript in trachea and mammary gland; in addition to these tissues, RT-PCR showed expression in lung. Recombinant CLCA2 was expressed in mammalian cells as a 120-kD primary translation product that was cleaved into an 86-kD N-terminal polypeptide and a 34-kD C-terminal polypeptide, both of which were associated with the outer cell surface. Expression of recombinant CLCA2 in HEK 293 cells resulted in a slightly outwardly rectifying anion conductance that was increased in the presence of



the calcium ionophore ionomycin and inhibited by DIDS, dithiothreitol, niflumic acid, and tamoxifen. By radiation hybrid analysis, Gruber and Pauli (1999) determined that the CLCA2 and CLCA3 genes map to 1p31–p22, where the CLCA1 gene had been assigned. Thus, all human CLCA family members known to that time were shown to be clustered on the short arm of chromosome 1 despite their moderately low levels of sequence homology and their heterogeneous expression patterns.

[32679] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32680] Gruber, A. D.; Pauli, B. U. : Clustering of the human CLCA gene family on the short arm of chromosome 1 (1p22–31). *Genome* 42: 1030–1032, 1999. ; and

[32681] Gruber, A. D.; Schreur, K. D.; Ji, H.–L.; Fuller, C. M.; Pauli, B. U. : Molecular cloning and transmembrane structure of hCLCA2 from human lung, trachea, and mammary gland. *Am. J. Phys.*

[32682] Further studies establishing the function and utilities of CLCA2 are found in John Hopkins OMIM database record ID 604003, and in cited publications numbered 739 and 8199 listed in the bibliography section hereinbelow, which

are also hereby incorporated by reference. Pituitary Tumor-transforming 1 Interacting Protein (PTTG1IP, Accession NM\_004339) is another VGAM851 host target gene. PTTG1IP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PTTG1IP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTTG1IP BINDING SITE, designated SEQ ID:10540, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32683] Another function of VGAM851 is therefore inhibition of Pituitary Tumor-transforming 1 Interacting Protein (PTTG1IP, Accession NM\_004339), a gene which facilitates the translocation of PTTG to the nucleus. Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTTG1IP. The function of PTTG1IP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM131. Kell Blood Group Precursor (McLeod phenotype) (XK, Accession NM\_021083) is an-

other VGAM851 host target gene. XK BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by XK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XK BINDING SITE, designated SEQ ID:22063, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32684] Another function of VGAM851 is therefore inhibition of Kell Blood Group Precursor (McLeod phenotype) (XK, Accession NM\_021083). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with XK. DKFZp564K142 (Accession NM\_032121) is another VGAM851 host target gene. DKFZp564K142 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp564K142, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp564K142 BINDING SITE, designated SEQ ID:25807, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM

RNA, also designated SEQ ID:3562.

[32685] Another function of VGAM851 is therefore inhibition of DKFZp564K142 (Accession NM\_032121). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp564K142. FLJ13197 (Accession NM\_024614) is another VGAM851 host target gene. FLJ13197 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13197, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13197 BINDING SITE, designated SEQ ID:23876, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32686] Another function of VGAM851 is therefore inhibition of FLJ13197 (Accession NM\_024614). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13197. KIAA0186 (Accession NM\_021067) is another VGAM851 host target gene. KIAA0186 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0186, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0186 BINDING SITE, designated SEQ ID:22040, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32687] Another function of VGAM851 is therefore inhibition of KIAA0186 (Accession NM\_021067). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0186. MGC4562 (Accession NM\_133375) is another VGAM851 host target gene. MGC4562 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC4562, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4562 BINDING SITE, designated SEQ ID:28497, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32688] Another function of VGAM851 is therefore inhibition of MGC4562 (Accession NM\_133375). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with MGC4562. LOC151258 (Accession XM\_087146) is another VGAM851 host target gene. LOC151258 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC151258, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151258 BINDING SITE, designated SEQ ID:39091, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32689] Another function of VGAM851 is therefore inhibition of LOC151258 (Accession XM\_087146). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151258. LOC157798 (Accession XM\_098827) is another VGAM851 host target gene. LOC157798 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC157798, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC157798 BINDING SITE, designated SEQ ID:41845, to

the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32690] Another function of VGAM851 is therefore inhibition of LOC157798 (Accession XM\_098827). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC157798. LOC200803 (Accession XM\_114299) is another VGAM851 host target gene. LOC200803 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200803, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200803 BINDING SITE, designated SEQ ID:42855, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32691] Another function of VGAM851 is therefore inhibition of LOC200803 (Accession XM\_114299). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200803. LOC256642 (Accession XM\_172797) is another VGAM851 host target gene. LOC256642 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC256642, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256642 BINDING SITE, designated SEQ ID:46080, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32692] Another function of VGAM851 is therefore inhibition of LOC256642 (Accession XM\_172797). Accordingly, utilities of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256642. LOC89932 (Accession XM\_027341) is another VGAM851 host target gene. LOC89932 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC89932, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC89932 BINDING SITE, designated SEQ ID:30493, to the nucleotide sequence of VGAM851 RNA, herein designated VGAM RNA, also designated SEQ ID:3562.

[32693] Another function of VGAM851 is therefore inhibition of LOC89932 (Accession XM\_027341). Accordingly, utilities



of VGAM851 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC89932. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 852 (VGAM852) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32694] VGAM852 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM852 was detected is described hereinabove with reference to Figs. 1–8.

[32695] VGAM852 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Molluscum Contagiosum Virus. VGAM852 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32696] VGAM852 gene encodes a VGAM852 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM852 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM852 precursor RNA is designated SEQ ID:838, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:838 is located at position 135041 relative to the genome of Moluscum Contagiosum Virus.

[32697] VGAM852 precursor RNA folds onto itself, forming VGAM852 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32698] An enzyme complex designated DICER COMPLEX, `dices` the VGAM852 folded precursor RNA into VGAM852 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 83%) nucleotide sequence of VGAM852 RNA is designated SEQ ID:3563, and

is provided hereinbelow with reference to the sequence listing part.

[32699] VGAM852 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM852 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM852 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32700] VGAM852 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM852 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM852 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM852 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM852 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32701] The complementary binding of VGAM852 RNA, herein designated VGAM RNA, to host target binding sites on VGAM852 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM852 host target RNA into VGAM852 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32702] It is appreciated that VGAM852 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM852 host target genes. The mRNA of each one of this plurality of VGAM852 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM852 RNA, herein designated VGAM RNA, and which when bound by VGAM852 RNA causes inhibition of translation of respective one or more VGAM852 host target proteins.

[32703] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM852 gene, herein designated VGAM GENE, on one or more VGAM852 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32704] It is yet further appreciated that a function of VGAM852 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM852 include diagnosis, prevention and treatment of viral infection by Mollusum Contagiosum Virus. Specific functions, and accordingly utilities, of VGAM852 correlate with, and may be deduced from, the identity of the host target genes which VGAM852 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32705] Nucleotide sequences of the VGAM852 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM852 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM852 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM852 are further described hereinbelow with reference to Table 1.

[32706] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM852 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM852 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32707] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM852 gene, herein designated VGAM is inhibition of expression of VGAM852 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM852 correlate with, and may be deduced from, the identity of the target genes which VGAM852 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32708] Potassium Voltage-gated Channel, Shaker-related Subfamily, Beta Member 2 (KCNAB2, Accession NM\_003636) is a VGAM852 host target gene. KCNAB2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KCNAB2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KCNAB2 BINDING SITE, designated SEQ ID:9705, to the nucleotide sequence of VGAM852 RNA, herein designated VGAM RNA, also designated SEQ ID:3563.

[32709] A function of VGAM852 is therefore inhibition of Potassium Voltage-gated Channel, Shaker-related Subfamily, Beta Member 2 (KCNAB2, Accession NM\_003636), a gene which is the beta subunit of shaker voltage-gated potassium channels. Accordingly, utilities of VGAM852 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNAB2. The function of KCNAB2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM659. Lactotransferrin (LTF, Accession NM\_002343) is another VGAM852 host target gene. LTF BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LTF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LTF BINDING SITE, designated SEQ ID:8142, to the nucleotide sequence of VGAM852 RNA, herein designated VGAM RNA, also designated SEQ ID:3563.

[32710] Another function of VGAM852 is therefore inhibition of Lactotransferrin (LTF, Accession NM\_002343), a gene which is an iron binding transport protein. Accordingly, utilities of VGAM852 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LTF. The function of LTF has been established by previous studies. *Haemophilus influenzae* is a major cause of otitis media and other respiratory tract disease in chil-



dren. The pathogenesis of the disease begins with colonization of the upper respiratory mucosa, a process that involves evasion of local immune mechanisms and adherence to epithelial cells. Several studies demonstrated that human milk is protective against *H. influenzae* colonization and disease. Qiu et al. (1998) examined the effect of human milk on 2 autotransported proteins of *H. influenzae* that are presumed to facilitate colonization: IgA1 protease and Hap adhesin. They found that human milk lactoferrin efficiently extracted the IgA1 protease preprotein from the bacterial outer membrane. In addition, lactoferrin specifically degraded the Hap adhesin and abolished Hap-mediated adherence. The results suggested that human milk lactoferrin attenuates the pathogenic potential of *H. influenzae* by selectively inactivating IgA1 protease and Hap, thereby interfering with colonization. They suggested that future studies should examine the therapeutic potential of lactoferrin, perhaps as a supplement in infant formulas. Human T-cell leukemia virus-1 (OMIM Ref. No. HTLV-1) causes T-cell leukemia and lymphoma and is clustered in certain geographic areas. Like HIV-1 infection, HTLV-1 infection can be transmitted vertically through breast milk. Refraining

from breast feeding was found to efficiently block mother-to-infant transmission in southwestern Japan. Moriuchi and Moriuchi (2001) observed a dose-dependent enhancement of HTLV-1 replication by transactivating the viral long terminal repeat in cells stimulated with human or bovine lactoferrin. Lactoferrin also accelerated transmission to uninfected cord blood mononuclear cells. Moriuchi and Moriuchi (2001) confirmed that lactoferrin inhibits HIV-1 replication and showed that it does so by nonspecifically blocking viral fusion to cells

[32711] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32712] Qiu, J.; Hendrixson, D. R.; Baker, E. N.; Murphy, T. F.; St. Geme, J. W., III; Plaut, A. G. : Human milk lactoferrin inactivates two putative colonization factors expressed by *Haemophilus influenzae*. *Proc. Nat. Acad. Sci.* 95: 12641-12646, 1998. ; and

[32713] Moriuchi, M.; Moriuchi, H. : A milk protein lactoferrin enhances human T cell leukemia virus type I and suppresses HIV-1 infection. *J. Immun.* 166: 4231-4236, 2001.

[32714] Further studies establishing the function and utilities of LTF are found in John Hopkins OMIM database record ID

150210, and in cited publications numbered 11339–11348 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ20294 (Accession NM\_017749) is another VGAM852 host target gene. FLJ20294 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20294, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20294 BINDING SITE, designated SEQ ID:19344, to the nucleotide sequence of VGAM852 RNA, herein designated VGAM RNA, also designated SEQ ID:3563.

[32715] Another function of VGAM852 is therefore inhibition of FLJ20294 (Accession NM\_017749). Accordingly, utilities of VGAM852 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20294. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 853 (VGAM853) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32716] VGAM853 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM853 was detected is described hereinabove with reference to Figs. 1–8.

[32717] VGAM853 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ectromelia Virus.

VGAM853 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32718] VGAM853 gene encodes a VGAM853 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM853 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM853 precursor RNA is designated SEQ ID:839, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:839 is located at position 202536 relative to the genome of Ectromelia Virus.

[32719] VGAM853 precursor RNA folds onto itself, forming VGAM853 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

`hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32720] An enzyme complex designated DICER COMPLEX, `dices` the VGAM853 folded precursor RNA into VGAM853 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM853 RNA is designated SEQ ID:3564, and is provided hereinbelow with reference to the sequence listing part.

[32721] VGAM853 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM853 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM853 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN

CODING and 3`UTR respectively.

[32722] VGAM853 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM853 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM853 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM853 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM853 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32723] The complementary binding of VGAM853 RNA, herein designated VGAM RNA, to host target binding sites on VGAM853 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM853 host target RNA into VGAM853 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32724] It is appreciated that VGAM853 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM853 host target genes. The mRNA of each one of this plurality of VGAM853 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM853 RNA, herein designated VGAM RNA, and which when bound by VGAM853 RNA causes inhibition of translation of respective one or more VGAM853 host target proteins.

[32725] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM853 gene, herein designated VGAM GENE, on one or more VGAM853 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32726] It is yet further appreciated that a function of VGAM853 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM853 include diagnosis, prevention and treatment of viral infection by Ectromelia Virus. Specific functions, and accordingly utilities, of VGAM853 correlate with, and may be deduced from, the identity of the host target genes which VGAM853 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32727] Nucleotide sequences of the VGAM853 precursor RNA,



herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM853 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM853 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM853 are further  
described hereinbelow with reference to Table 1.

[32728] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM853 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM853 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[32729] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM853 gene, herein designated VGAM is  
inhibition of expression of VGAM853 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM853 correlate with, and may be deduced  
from, the identity of the target genes which VGAM853  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[32730] LOC168512 (Accession XM\_095148) is a VGAM853 host  
target gene. LOC168512 BINDING SITE is HOST TARGET

binding site found in the 5` untranslated region of mRNA encoded by LOC168512, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC168512 BINDING SITE, designated SEQ ID:40251, to the nucleotide sequence of VGAM853 RNA, herein designated VGAM RNA, also designated SEQ ID:3564.

[32731] A function of VGAM853 is therefore inhibition of LOC168512 (Accession XM\_095148). Accordingly, utilities of VGAM853 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC168512. LOC200059 (Accession XM\_114104) is another VGAM853 host target gene. LOC200059 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC200059, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200059 BINDING SITE, designated SEQ ID:42699, to the nucleotide sequence of VGAM853 RNA, herein designated VGAM RNA, also designated SEQ ID:3564.

[32732] Another function of VGAM853 is therefore inhibition of

LOC200059 (Accession XM\_114104). Accordingly, utilities of VGAM853 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200059. LOC81537 (Accession NM\_030791) is another VGAM853 host target gene. LOC81537 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC81537, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC81537 BINDING SITE, designated SEQ ID:25087, to the nucleotide sequence of VGAM853 RNA, herein designated VGAM RNA, also designated SEQ ID:3564.

[32733] Another function of VGAM853 is therefore inhibition of LOC81537 (Accession NM\_030791). Accordingly, utilities of VGAM853 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC81537. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 854 (VGAM854) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[32734] VGAM854 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM854 was detected is described hereinabove with reference to Figs. 1–8.

[32735] VGAM854 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Amsacta Moorei Entomopoxvirus. VGAM854 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32736] VGAM854 gene encodes a VGAM854 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM854 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM854 precursor RNA is designated SEQ ID:840, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:840 is located at position 79626 relative to the genome of Amsacta Moorei Entomopoxvirus.

[32737] VGAM854 precursor RNA folds onto itself, forming VGAM854 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[32738] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM854 folded precursor RNA into VGAM854 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 76%) nucleotide se-  
quence of VGAM854 RNA is designated SEQ ID:3565, and  
is provided hereinbelow with reference to the sequence  
listing part.

[32739] VGAM854 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM854 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM854 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32740] VGAM854 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM854 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM854 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM854 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM854 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[32741] The complementary binding of VGAM854 RNA, herein designated VGAM RNA, to host target binding sites on VGAM854 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM854 host target RNA into VGAM854 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32742] It is appreciated that VGAM854 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM854 host target genes. The mRNA of each one of this plurality of VGAM854 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM854 RNA, herein designated VGAM RNA, and which when bound by VGAM854 RNA causes inhibition of translation of respective one or more VGAM854 host target proteins.

[32743] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM854 gene, herein designated VGAM GENE, on one or

more VGAM854 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32744] It is yet further appreciated that a function of VGAM854 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of viral infection by Amsacta Moorei Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM854 correlate with, and may be deduced from, the identity of the host target genes which VGAM854 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.



- [32745] Nucleotide sequences of the VGAM854 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM854 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM854 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM854 are further described hereinbelow with reference to Table 1.
- [32746] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM854 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM854 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [32747] As mentioned hereinabove with reference to Fig. 1, a function of VGAM854 gene, herein designated VGAM is inhibition of expression of VGAM854 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM854 correlate with, and may be deduced from, the identity of the target genes which VGAM854 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [32748] Egl Nine Homolog 1 (C. elegans) (EGLN1, Accession

NM\_022051) is a VGAM854 host target gene. EGLN1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EGLN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGLN1 BINDING SITE, designated SEQ ID:22581, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32749] A function of VGAM854 is therefore inhibition of Egl Nine Homolog 1 (*C. elegans*) (EGLN1, Accession NM\_022051), a gene which is expressed in the cytoplasm of arterial smooth muscle cells. Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGLN1. The function of EGLN1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM216.KIP2 (Accession NM\_006383) is another VGAM854 host target gene. KIP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIP2 BINDING SITE, designated SEQ ID:13087, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32750] Another function of VGAM854 is therefore inhibition of KIP2 (Accession NM\_006383). Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIP2. Myotubularin Related Protein 8 (MTMR8, Accession NM\_015458) is another VGAM854 host target gene. MTMR8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MTMR8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MTMR8 BINDING SITE, designated SEQ ID:17743, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32751] Another function of VGAM854 is therefore inhibition of Myotubularin Related Protein 8 (MTMR8, Accession NM\_015458), a gene which could be a tyrosine-

phosphatase. Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MTMR8. The function of MTMR8 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM379. Ubiquitin-conjugating Enzyme E2A (RAD6 homolog) (UBE2A, Accession NM\_003336) is another VGAM854 host target gene. UBE2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2A BINDING SITE, designated SEQ ID:9340, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32752] Another function of VGAM854 is therefore inhibition of Ubiquitin-conjugating Enzyme E2A (RAD6 homolog) (UBE2A, Accession NM\_003336), a gene which catalyzes the covalent attachment of ubiquitin to other proteins and is required for postreplication repair of uv-damaged dna. Accordingly, utilities of VGAM854 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with UBE2A. The function of UBE2A and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM294. Basic Leucine Zipper Nuclear Factor 1 (JEM-1) (BLZF1, Accession NM\_003666) is another VGAM854 host target gene. BLZF1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BLZF1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLZF1 BINDING SITE, designated SEQ ID:9749, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32753] Another function of VGAM854 is therefore inhibition of Basic Leucine Zipper Nuclear Factor 1 (JEM-1) (BLZF1, Accession NM\_003666). Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLZF1. FLJ20069 (Accession NM\_017651) is another VGAM854 host target gene. FLJ20069 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by FLJ20069, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20069 BINDING SITE, designated SEQ ID:19160, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32754] Another function of VGAM854 is therefore inhibition of FLJ20069 (Accession NM\_017651). Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20069. LCE (Accession NM\_024090) is another VGAM854 host target gene. LCE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LCE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LCE BINDING SITE, designated SEQ ID:23533, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32755] Another function of VGAM854 is therefore inhibition of LCE (Accession NM\_024090). Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with LCE.

LOC147219 (Accession XM\_097214) is another VGAM854 host target gene. LOC147219 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147219, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147219 BINDING SITE, designated SEQ ID:40821, to the nucleotide sequence of VGAM854 RNA, herein designated VGAM RNA, also designated SEQ ID:3565.

[32756] Another function of VGAM854 is therefore inhibition of LOC147219 (Accession XM\_097214). Accordingly, utilities of VGAM854 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147219. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 855 (VGAM855) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32757] VGAM855 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM855 was detected is described hereinabove with reference to Figs. 1–8.

[32758] VGAM855 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM855 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32759] VGAM855 gene encodes a VGAM855 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM855 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM855 precursor RNA is designated SEQ ID:841, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:841 is located at position 45064 relative to the genome of African Swine Fever Virus.

[32760] VGAM855 precursor RNA folds onto itself, forming VGAM855 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA



genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32761] An enzyme complex designated DICER COMPLEX, `dices` the VGAM855 folded precursor RNA into VGAM855 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM855 RNA is designated SEQ ID:3566, and is provided hereinbelow with reference to the sequence listing part.

[32762] VGAM855 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM855 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM855 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32763] VGAM855 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM855 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM855 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM855 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM855 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32764] The complementary binding of VGAM855 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM855 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM855 host target RNA into VGAM855 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32765] It is appreciated that VGAM855 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM855 host target genes. The mRNA of each one of this plurality of VGAM855 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM855 RNA, herein designated VGAM RNA, and which when bound by VGAM855 RNA causes inhibition of translation of respective one or more VGAM855 host target proteins.

[32766] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM855 gene, herein designated VGAM GENE, on one or more VGAM855 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32767] It is yet further appreciated that a function of VGAM855 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM855 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus. Specific functions, and accordingly utilities, of VGAM855 correlate with, and may be deduced from, the identity of the host target genes which VGAM855 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32768] Nucleotide sequences of the VGAM855 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

5' duced 5' VGAM855 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM855 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM855 are further described hereinbelow with reference to Table 1.

[32769] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM855 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM855 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32770] As mentioned hereinabove with reference to Fig. 1, a function of VGAM855 gene, herein designated VGAM is inhibition of expression of VGAM855 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM855 correlate with, and may be deduced from, the identity of the target genes which VGAM855 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32771] Ets Homologous Factor (EHF, Accession NM\_012153) is a VGAM855 host target gene. EHF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by EHF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EHF BINDING SITE, designated SEQ ID:14451, to the nucleotide sequence of VGAM855 RNA, herein designated VGAM RNA, also designated SEQ ID:3566.

[32772] A function of VGAM855 is therefore inhibition of Ets Homologous Factor (EHF, Accession NM\_012153), a gene which is Member of the ESE subfamily of Ets transcription factors. Accordingly, utilities of VGAM855 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EHF. The function of EHF has been established by previous studies. By searching an EST database, Kas et al. (2000) identified an EST with sequence similarity to the ETS domain of human ESE1 (ELF3; 602191). They obtained a full-length cDNA encoding EHF, which they called ESE3, by using 5-prime RACE on human prostate cDNA. RT-PCR analysis identified 2 alternatively spliced forms of ESE3, ESE3a and ESE3b. Sequence analysis predicted that ESE3a encodes a 277-amino acid protein with a molecular mass of 32.3 kD, while ESE3b encodes a 300-amino acid protein with a molecular mass of

34.9 kD. The C-terminal ETS domain of ESE3 is 84% and 65% identical to the ETS domains of ESE1 and ESE2 (ELF5; 605169), respectively. Northern blot analysis detected a 5.9-kb ESE3 transcript in pancreas and prostate, with lower levels detected in kidney and colon. Dot blot analysis detected high levels of ESE3 expression in salivary gland, prostate, and trachea, with lower levels detected in colon, mammary gland, pancreas, lung, stomach, appendix, fetal kidney, and fetal lung. Using RT-PCR on primary and tumor-derived cell lines, the authors detected expression of ESE3 in tumor cells of epithelial origin. Gel-shift experiments showed binding of ESE3 to 3 high-affinity binding sites in the MET (OMIM Ref. No. 164860) promoter. Cotransfection of ESE3 expression vectors with a MET promoter-luciferase reporter construct demonstrated that both ESE3a and ESE3b act as transcriptional activators on this promoter. Kleinbaum et al. (1999) mapped the EHF gene to 11p12 by somatic cell hybrid analysis and FISH.

[32773] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32774] Kas, K.; Finger, E.; Grall, F.; Gu, X.; Akbarali, Y.; Boltax, J.;

Weiss, A.; Oettgen, P.; Kapeller, R.; Libermann, T. A. : ESE-3, a novel member of an epithelium-specific Ets transcription factor subfamily, demonstrates different target gene specificity from ESE-1. J. Biol. Chem. 275: 2986-2998, 2000. ; and

[32775] Kleinbaum, L. A.; Duggan, C.; Ferreira, E.; Coffey, G. P.; Buttice, G.; Burton, F. H. : Human chromosomal localization, tissue/tumor expression, and regulatory function of the ets fami.

[32776] Further studies establishing the function and utilities of EHF are found in John Hopkins OMIM database record ID 605439, and in cited publications numbered 4792-4793 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Estrogen Receptor 1 (ESR1, Accession NM\_000125) is another VGAM855 host target gene. ESR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESR1 BINDING SITE, designated SEQ ID:5598, to the nucleotide sequence of VGAM855 RNA, herein designated VGAM RNA, also designated SEQ ID:3566.



[32777] Another function of VGAM855 is therefore inhibition of Estrogen Receptor 1 (ESR1, Accession NM\_000125), a gene which involved in hormone-mediated inhibition of gene expression. Accordingly, utilities of VGAM855 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESR1. The function of ESR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM695.FLJ11053 (Accession XM\_114194) is another VGAM855 host target gene. FLJ11053 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11053, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11053 BINDING SITE, designated SEQ ID:42776, to the nucleotide sequence of VGAM855 RNA, herein designated VGAM RNA, also designated SEQ ID:3566.

[32778] Another function of VGAM855 is therefore inhibition of FLJ11053 (Accession XM\_114194). Accordingly, utilities of VGAM855 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11053.

FLJ11827 (Accession NM\_025093) is another VGAM855 host target gene. FLJ11827 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11827, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11827 BINDING SITE, designated SEQ ID:24720, to the nucleotide sequence of VGAM855 RNA, herein designated VGAM RNA, also designated SEQ ID:3566.

[32779] Another function of VGAM855 is therefore inhibition of FLJ11827 (Accession NM\_025093). Accordingly, utilities of VGAM855 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11827. LOC253664 (Accession XM\_170673) is another VGAM855 host target gene. LOC253664 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253664, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253664 BINDING SITE, designated SEQ ID:45447, to the nucleotide sequence of VGAM855 RNA, herein designated VGAM RNA,

also designated SEQ ID:3566.

[32780] Another function of VGAM855 is therefore inhibition of LOC253664 (Accession XM\_170673). Accordingly, utilities of VGAM855 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253664. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 856 (VGAM856) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32781] VGAM856 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM856 was detected is described hereinabove with reference to Figs. 1–8.

[32782] VGAM856 gene, herein designated VGAM GENE, is a viral gene contained in the genome of African Swine Fever Virus. VGAM856 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32783] VGAM856 gene encodes a VGAM856 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM856 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM856 precursor RNA is designated SEQ ID:842, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:842 is located at position 43493 relative to the genome of African Swine Fever Virus.

[32784] VGAM856 precursor RNA folds onto itself, forming VGAM856 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32785] An enzyme complex designated DICER COMPLEX, `dices` the VGAM856 folded precursor RNA into VGAM856 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 51%) nucleotide sequence of VGAM856 RNA is designated SEQ ID:3567, and is provided hereinbelow with reference to the sequence listing part.

[32786] VGAM856 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM856 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM856 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[32787] VGAM856 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM856 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM856 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM856 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM856 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32788] The complementary binding of VGAM856 RNA, herein designated VGAM RNA, to host target binding sites on VGAM856 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM856 host target RNA into VGAM856 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32789] It is appreciated that VGAM856 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM856 host target genes. The mRNA of

each one of this plurality of VGAM856 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM856 RNA, herein designated VGAM RNA, and which when bound by VGAM856 RNA causes inhibition of translation of respective one or more VGAM856 host target proteins.

[32790] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM856 gene, herein designated VGAM GENE, on one or more VGAM856 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[32791] It is yet further appreciated that a function of VGAM856 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of viral infection by African Swine Fever Virus. Specific functions, and accordingly utilities, of VGAM856 correlate with, and may be deduced from, the identity of the host target genes which VGAM856 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32792] Nucleotide sequences of the VGAM856 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM856 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM856 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM856 are further described hereinbelow with reference to Table 1.

[32793] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM856 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM856 RNA, herein desig-



nated VGAM RNA, are described hereinbelow with reference to Table 2.

[32794] As mentioned hereinabove with reference to Fig. 1, a function of VGAM856 gene, herein designated VGAM is inhibition of expression of VGAM856 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM856 correlate with, and may be deduced from, the identity of the target genes which VGAM856 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32795] Sparc/osteonectin, Cwcv and Kazal-like Domains Proteoglycan (testican) (SPOCK, Accession XM\_031696) is a VGAM856 host target gene. SPOCK BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SPOCK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPOCK BINDING SITE, designated SEQ ID:31455, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32796] A function of VGAM856 is therefore inhibition of Sparc/osteonectin, Cwcv and Kazal-like Domains Proteoglycan

(testican) (SPOCK, Accession XM\_031696). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPOCK. BOP (Accession XM\_097915) is another VGAM856 host target gene. BOP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BOP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BOP BINDING SITE, designated SEQ ID:41207, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32797] Another function of VGAM856 is therefore inhibition of BOP (Accession XM\_097915). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BOP. CHRNA7 (cholinergic receptor, nicotinic, alpha polypeptide 7, exons 5–10) and FAM7A (family with sequence similarity 7A, exons A–E) Fusion (CHRFAM7A, Accession XM\_170784) is another VGAM856 host target gene. CHRFAM7A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

CHRFAM7A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CHRFAM7A BINDING SITE, designated SEQ ID:45552, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32798] Another function of VGAM856 is therefore inhibition of CHRNA7 (cholinergic receptor, nicotinic, alpha polypeptide 7, exons 5–10) and FAM7A (family with sequence similarity 7A, exons A–E) Fusion (CHRFAM7A, Accession XM\_170784). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CHRFAM7A. KIAA1416 (Accession XM\_098762) is another VGAM856 host target gene. KIAA1416 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1416, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1416 BINDING SITE, designated SEQ ID:41799, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ

ID:3567.

[32799] Another function of VGAM856 is therefore inhibition of KIAA1416 (Accession XM\_098762). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1416. LBP-9 (Accession NM\_014553) is another VGAM856 host target gene. LBP-9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LBP-9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LBP-9 BINDING SITE, designated SEQ ID:15878, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32800] Another function of VGAM856 is therefore inhibition of LBP-9 (Accession NM\_014553). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LBP-9. LOC132625 (Accession XM\_067946) is another VGAM856 host target gene. LOC132625 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC132625, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC132625 BINDING SITE, designated SEQ ID:37371, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32801] Another function of VGAM856 is therefore inhibition of LOC132625 (Accession XM\_067946). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC132625. LOC148811 (Accession XM\_086326) is another VGAM856 host target gene. LOC148811 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148811, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148811 BINDING SITE, designated SEQ ID:38597, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32802] Another function of VGAM856 is therefore inhibition of LOC148811 (Accession XM\_086326). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC148811. LOC256733 (Accession XM\_173116) is another VGAM856 host target gene. LOC256733 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256733, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256733 BINDING SITE, designated SEQ ID:46367, to the nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32803] Another function of VGAM856 is therefore inhibition of LOC256733 (Accession XM\_173116). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256733. LOC90936 (Accession XM\_034953) is another VGAM856 host target gene. LOC90936 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90936, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90936 BINDING SITE, designated SEQ ID:32188, to the

nucleotide sequence of VGAM856 RNA, herein designated VGAM RNA, also designated SEQ ID:3567.

[32804] Another function of VGAM856 is therefore inhibition of LOC90936 (Accession XM\_034953). Accordingly, utilities of VGAM856 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90936. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 857 (VGAM857) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32805] VGAM857 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM857 was detected is described hereinabove with reference to Figs. 1–8.

[32806] VGAM857 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ectromelia Virus. VGAM857 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32807] VGAM857 gene encodes a VGAM857 precursor RNA,

herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM857 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM857 precursor RNA is designated SEQ ID:843, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:843 is located at position 134388 relative to the genome of Ectromelia Virus.

[32808] VGAM857 precursor RNA folds onto itself, forming VGAM857 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32809] An enzyme complex designated DICER COMPLEX, `dices` the VGAM857 folded precursor RNA into VGAM857 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short



~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM857 RNA is designated SEQ ID:3568, and is provided hereinbelow with reference to the sequence listing part.

[32810] VGAM857 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM857 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM857 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32811] VGAM857 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM857 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM857 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding

sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM857 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM857 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[32812] The complementary binding of VGAM857 RNA, herein designated VGAM RNA, to host target binding sites on VGAM857 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM857 host target RNA into VGAM857 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32813] It is appreciated that VGAM857 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents

a plurality of VGAM857 host target genes. The mRNA of each one of this plurality of VGAM857 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM857 RNA, herein designated VGAM RNA, and which when bound by VGAM857 RNA causes inhibition of translation of respective one or more VGAM857 host target proteins.

[32814] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM857 gene, herein designated VGAM GENE, on one or more VGAM857 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G.,

`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[32815] It is yet further appreciated that a function of VGAM857 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM857 include diagnosis, prevention and treatment of viral infection by Ectromelia Virus. Specific functions, and accordingly utilities, of VGAM857 correlate with, and may be deduced from, the identity of the host target genes which VGAM857 binds and inhibits, and the function of these host target genes, as elaborated herein–below.

[32816] Nucleotide sequences of the VGAM857 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM857 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM857 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM857 are further described hereinbelow with reference to Table 1.

[32817] Nucleotide sequences of host target binding sites, such as BINDING SITE–I, BINDING SITE–II and BINDING SITE–III of Fig. 1, found on VGAM857 host target RNA, and schematic representation of the complementarity of each of these

host target binding sites to VGAM857 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32818] As mentioned hereinabove with reference to Fig. 1, a function of VGAM857 gene, herein designated VGAM is inhibition of expression of VGAM857 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM857 correlate with, and may be deduced from, the identity of the target genes which VGAM857 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32819] Endothelin 3 (EDN3, Accession NM\_000114) is a VGAM857 host target gene. EDN3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EDN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EDN3 BINDING SITE, designated SEQ ID:5583, to the nucleotide sequence of VGAM857 RNA, herein designated VGAM RNA, also designated SEQ ID:3568.

[32820] A function of VGAM857 is therefore inhibition of Endothelin 3 (EDN3, Accession NM\_000114). Accordingly, utilities

of VGAM857 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EDN3. DKFZP564F013 (Accession XM\_168479) is another VGAM857 host target gene. DKFZP564F013 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564F013, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564F013 BINDING SITE, designated SEQ ID:45203, to the nucleotide sequence of VGAM857 RNA, herein designated VGAM RNA, also designated SEQ ID:3568.

[32821] Another function of VGAM857 is therefore inhibition of DKFZP564F013 (Accession XM\_168479). Accordingly, utilities of VGAM857 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564F013. Epsin 2 (EPN2, Accession NM\_014964) is another VGAM857 host target gene. EPN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EPN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPN2 BINDING

SITE, designated SEQ ID:17350, to the nucleotide sequence of VGAM857 RNA, herein designated VGAM RNA, also designated SEQ ID:3568.

[32822] Another function of VGAM857 is therefore inhibition of Epsin 2 (EPN2, Accession NM\_014964). Accordingly, utilities of VGAM857 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPN2. KIAA1486 (Accession XM\_041126) is another VGAM857 host target gene. KIAA1486 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1486, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1486 BINDING SITE, designated SEQ ID:33463, to the nucleotide sequence of VGAM857 RNA, herein designated VGAM RNA, also designated SEQ ID:3568.

[32823] Another function of VGAM857 is therefore inhibition of KIAA1486 (Accession XM\_041126). Accordingly, utilities of VGAM857 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1486. Ubiquitin Specific Protease 15 (USP15, Accession NM\_006313) is another VGAM857 host target gene.

USP15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by USP15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USP15 BINDING SITE, designated SEQ ID:13005, to the nucleotide sequence of VGAM857 RNA, herein designated VGAM RNA, also designated SEQ ID:3568.

[32824] Another function of VGAM857 is therefore inhibition of Ubiquitin Specific Protease 15 (USP15, Accession NM\_006313). Accordingly, utilities of VGAM857 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USP15. LOC152317 (Accession XM\_098189) is another VGAM857 host target gene. LOC152317 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152317 BINDING SITE, designated SEQ ID:41468, to the nucleotide sequence of VGAM857 RNA, herein designated VGAM RNA, also desig-



nated SEQ ID:3568.

[32825] Another function of VGAM857 is therefore inhibition of LOC152317 (Accession XM\_098189). Accordingly, utilities of VGAM857 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152317. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 858 (VGAM858) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32826] VGAM858 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM858 was detected is described hereinabove with reference to Figs. 1–8.

[32827] VGAM858 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ectromelia Virus. VGAM858 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32828] VGAM858 gene encodes a VGAM858 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM858 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM858 precursor RNA is designated SEQ ID:844, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:844 is located at position 132888 relative to the genome of Ectromelia Virus.

[32829] VGAM858 precursor RNA folds onto itself, forming VGAM858 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32830] An enzyme complex designated DICER COMPLEX, `dices` the VGAM858 folded precursor RNA into VGAM858 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM858 RNA is designated SEQ ID:3569, and is provided hereinbelow with reference to the sequence listing part.

[32831] VGAM858 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM858 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM858 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32832] VGAM858 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM858 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM858 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM858 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM858 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[32833] The complementary binding of VGAM858 RNA, herein designated VGAM RNA, to host target binding sites on VGAM858 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM858 host target RNA into VGAM858 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32834] It is appreciated that VGAM858 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM858 host target genes. The mRNA of

each one of this plurality of VGAM858 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM858 RNA, herein designated VGAM RNA, and which when bound by VGAM858 RNA causes inhibition of translation of respective one or more VGAM858 host target proteins.

[32835] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM858 gene, herein designated VGAM GENE, on one or more VGAM858 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[32836] It is yet further appreciated that a function of VGAM858 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM858 include diagnosis, prevention and treatment of viral infection by Ectromelia Virus. Specific functions, and accordingly utilities, of VGAM858 correlate with, and may be deduced from, the identity of the host target genes which VGAM858 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32837] Nucleotide sequences of the VGAM858 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM858 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM858 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM858 are further described hereinbelow with reference to Table 1.

[32838] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM858 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM858 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[32839] As mentioned hereinabove with reference to Fig. 1, a function of VGAM858 gene, herein designated VGAM is inhibition of expression of VGAM858 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM858 correlate with, and may be deduced from, the identity of the target genes which VGAM858 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32840] KIAA0143 (Accession XM\_035825) is a VGAM858 host target gene. KIAA0143 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0143, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0143 BINDING SITE, designated SEQ ID:32351, to the nucleotide sequence of VGAM858 RNA, herein designated VGAM RNA, also designated SEQ ID:3569.

[32841] A function of VGAM858 is therefore inhibition of KIAA0143 (Accession XM\_035825). Accordingly, utilities of VGAM858 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA0143. Solute Carrier Family 26, Member 7 (SLC26A7, Accession NM\_052832) is another VGAM858 host target gene. SLC26A7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC26A7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC26A7 BINDING SITE, designated SEQ ID:27417, to the nucleotide sequence of VGAM858 RNA, herein designated VGAM RNA, also designated SEQ ID:3569.

[32842] Another function of VGAM858 is therefore inhibition of Solute Carrier Family 26, Member 7 (SLC26A7, Accession NM\_052832). Accordingly, utilities of VGAM858 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC26A7. LOC158292 (Accession XM\_098914) is another VGAM858 host target gene. LOC158292 BINDING SITE1 and LOC158292 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC158292, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-



illustrates the complementarity of the nucleotide sequences of LOC158292 BINDING SITE1 and LOC158292 BINDING SITE2, designated SEQ ID:41934 and SEQ ID:41935 respectively, to the nucleotide sequence of VGAM858 RNA, herein designated VGAM RNA, also designated SEQ ID:3569.

[32843] Another function of VGAM858 is therefore inhibition of LOC158292 (Accession XM\_098914). Accordingly, utilities of VGAM858 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158292. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 859 (VGAM859) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32844] VGAM859 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM859 was detected is described hereinabove with reference to Figs. 1–8.

[32845] VGAM859 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Camelpox Virus.

VGAM859 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32846] VGAM859 gene encodes a VGAM859 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM859 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM859 precursor RNA is designated SEQ ID:845, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:845 is located at position 126158 relative to the genome of Camelpox Virus.

[32847] VGAM859 precursor RNA folds onto itself, forming VGAM859 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32848] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM859 folded precursor RNA into VGAM859 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 83%) nucleotide sequence of VGAM859 RNA is designated SEQ ID:3570, and is provided hereinbelow with reference to the sequence listing part.

[32849] VGAM859 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM859 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM859 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32850] VGAM859 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM859 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM859 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM859 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM859 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32851] The complementary binding of VGAM859 RNA, herein designated VGAM RNA, to host target binding sites on VGAM859 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM859 host target RNA into VGAM859 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32852] It is appreciated that VGAM859 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM859 host target genes. The mRNA of each one of this plurality of VGAM859 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM859 RNA, herein designated VGAM RNA, and which when bound by VGAM859 RNA causes inhibition of translation of respective one or more VGAM859 host target proteins.

[32853] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM859 gene, herein designated VGAM GENE, on one or more VGAM859 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32854] It is yet further appreciated that a function of VGAM859 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of viral infection by Camelpox Virus. Specific functions, and accordingly utilities, of VGAM859 correlate with, and may be deduced from, the identity of the host target genes which VGAM859 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32855] Nucleotide sequences of the VGAM859 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM859 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM859 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM859 are further described hereinbelow with reference to Table 1.

[32856] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM859 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM859 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32857] As mentioned hereinabove with reference to Fig. 1, a function of VGAM859 gene, herein designated VGAM is inhibition of expression of VGAM859 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM859 correlate with, and may be deduced from, the identity of the target genes which VGAM859 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32858] A Disintegrin and Metalloproteinase Domain 22 (ADAM22, Accession NM\_021722) is a VGAM859 host target gene. ADAM22 BINDING SITE1 and ADAM22 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by ADAM22, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAM22 BIND-

ING SITE1 and ADAM22 BINDING SITE2, designated SEQ ID:22323 and SEQ ID:22325 respectively, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32859] A function of VGAM859 is therefore inhibition of A Disintegrin and Metalloproteinase Domain 22 (ADAM22, Accession NM\_021722), a gene which Member of ADAM family of zinc metalloproteases. Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADAM22. The function of ADAM22 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM81. Karyopherin Alpha 1 (importin alpha 5) (KPNA1, Accession XM\_087256) is another VGAM859 host target gene. KPNA1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KPNA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KPNA1 BINDING SITE, designated SEQ ID:39150, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ



ID:3570.

[32860] Another function of VGAM859 is therefore inhibition of Karyopherin Alpha 1 (importin alpha 5) (KPNA1, Accession XM\_087256), a gene which promotes docking of import substrates to the nuclear pore complex. Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KPNA1. The function of KPNA1 has been established by previous studies. Cortes et al. (1994) used the 2-hybrid protein interaction systems to isolate a protein that specifically interacts with RAG1 (OMIM Ref. No. 179615). The genes RAG1 and RAG2 (OMIM Ref. No. 179616) are able to activate V(D)J recombination when transfected into fibroblasts. Further, knockout mice for these 2 loci lack B and T cells. Several other ubiquitously expressed proteins are thought to be recruited in the recombination process. Among these are the genes affected in severe combined immune deficiency (e.g., OMIM Ref. No. also 600899) and genes involved in ds-DNA break repair. The human cDNA identified by Cortes et al. (1994) encodes a 489-amino acid polypeptide that shows striking similarity to the yeast SRP1 protein, a mutant allele which can suppress a mutation of RNA polymerase I. The authors obtained human

and mouse cDNA sequences which are 98% identical as proteins. When RAG1 and human SRP1 were cotransfected into 293T cells a stable complex of the 2 was observed. The authors speculated that because SRP1 appears to be bound to the nuclear envelope, the interaction with RAG1 may serve to localize that protein to the envelope as well. Conti et al. (1998) reported the crystal structure of a 50-kD fragment of the 60-kD yeast karyopherin alpha, in the absence and presence of a monopartite nuclear localization signal (NLS) peptide at 2.2-angstrom and 2.8-angstrom resolution, respectively. The structure showed a tandem array of 10 armadillo repeats, organized in a right-handed superhelix of helices. Binding of the NLS peptide occurred at 2 sites within a helical surface groove. The structure reveals the determinants of NLS specificity and suggested a model for the recognition of bipartite NLSs. By fluorescence in situ hybridization, Ayala-Madrigal et al. (2000) mapped the human KPNA1 gene to chromosome 3q21.

[32861] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32862] Ayala-Madrigal, M. L.; Doerr, S.; Ramirez-Duenas, M. L.;

Hansmann, I. : Assignment of karyopherin alpha 1 (KPNA1) to human chromosome band 3q21 by in situ hybridization. Cytogenet. Cell Genet. 90: 58–59, 2000. ; and

[32863] Conti, E.; Uy, M.; Leighton, L.; Blobel, G.; Kuriyan, J. : Crystallographic analysis of the recognition of a nuclear localization signal by the nuclear import factor karyopherin alpha.

[32864] Further studies establishing the function and utilities of KPNA1 are found in John Hopkins OMIM database record ID 600686, and in cited publications numbered 9973–9975 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Procollagen–proline, 2–oxoglutarate 4–dioxygenase (proline 4–hydroxylase), Alpha Polypeptide I (P4HA1, Accession NM\_000917) is another VGAM859 host target gene. P4HA1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by P4HA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P4HA1 BINDING SITE, designated SEQ ID:6624, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ

ID:3570.

[32865] Another function of VGAM859 is therefore inhibition of Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), Alpha Polypeptide I (P4HA1, Accession NM\_000917), a gene which catalyzes the formation of 4-hydroxyproline in collagen. Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P4HA1. The function of P4HA1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM260. Solute Carrier Family 1 (glutamate/neutral amino acid transporter), Member 4 (SLC1A4, Accession NM\_003038) is another VGAM859 host target gene. SLC1A4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC1A4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC1A4 BINDING SITE, designated SEQ ID:8999, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32866] Another function of VGAM859 is therefore inhibition of Solute Carrier Family 1 (glutamate/neutral amino acid transporter), Member 4 (SLC1A4, Accession NM\_003038), a gene which transports alanine, serine, cysteine, and threonine. exhibits sodium dependence. Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC1A4. The function of SLC1A4 has been established by previous studies. In a screening for cDNAs encoding proteins similar to the sodium-coupled glutamate transporter GLAST1, Hofmann et al. (1994) isolated a cDNA clone encoding a protein that turned out to be identical to the neutral amino acid transporter ASCT1 (Arriza et al., 1993; Shafqat et al., 1993). The new member of the GLAST-related transporter family did not transport glutamate or aspartate but alanine, serine, cysteine, and threonine instead. The open reading frame of 1,572 basepairs encodes 524 amino acid residues distributed over 8 exons spanning at least 40 kb of genomic DNA. The gene for ASCT1, designated SLC1A4, was assigned to 2p15-p13 by fluorescence in situ hybridization. The gene structure was not related to any previously characterized transporter gene. Zerangue and Kavanaugh (1996) found that the

ASCT1 transporter functions primarily as an amino acid exchanger. Transport is associated with a chloride channel activity that is thermodynamically uncoupled from amino acid transport.

[32867] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32868] Arriza, J. L.; Kavanaugh, M. P.; Fairman, W. A.; Wu, Y.-N.; Murdoch, G. H.; North, R. A.; Amara, S. G. : Cloning and expression of a human neutral amino acid transporter with structural similarity to the glutamate transporter gene family. J. Biol. Chem. 268: 15329–15332, 1993. ; and

[32869] Zerangue, N.; Kavanaugh, M. P. : ASCT–1 is a neutral amino acid exchanger with chloride channel activity. J. Biol. Chem. 271: 27991–27994, 1996.

[32870] Further studies establishing the function and utilities of SLC1A4 are found in John Hopkins OMIM database record ID 600229, and in cited publications numbered 7556–7559 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 20 Open Reading Frame 13 (C20orf13, Accession NM\_017714) is another VGAM859 host target

gene. C20orf13 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf13, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf13 BINDING SITE, designated SEQ ID:19298, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32871] Another function of VGAM859 is therefore inhibition of Chromosome 20 Open Reading Frame 13 (C20orf13, Accession NM\_017714). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf13. DIS3 (Accession NM\_014953) is another VGAM859 host target gene. DIS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DIS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DIS3 BINDING SITE, designated SEQ ID:17305, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32872] Another function of VGAM859 is therefore inhibition of DIS3 (Accession NM\_014953). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DIS3. DKFZp547A023 (Accession XM\_052065) is another VGAM859 host target gene. DKFZp547A023 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp547A023, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp547A023 BINDING SITE, designated SEQ ID:35945, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32873] Another function of VGAM859 is therefore inhibition of DKFZp547A023 (Accession XM\_052065). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp547A023. FLJ13072 (Accession XM\_117117) is another VGAM859 host target gene. FLJ13072 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ13072, corresponding to a HOST TARGET binding site such as BINDING



SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13072 BINDING SITE, designated SEQ ID:43237, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32874] Another function of VGAM859 is therefore inhibition of FLJ13072 (Accession XM\_117117). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13072. FLJ22794 (Accession XM\_166220) is another VGAM859 host target gene. FLJ22794 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ22794, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22794 BINDING SITE, designated SEQ ID:44038, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32875] Another function of VGAM859 is therefore inhibition of FLJ22794 (Accession XM\_166220). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22794.

Zinc Finger Protein 197 (ZNF197, Accession NM\_006991) is another VGAM859 host target gene. ZNF197 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF197, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF197 BINDING SITE, designated SEQ ID:13855, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32876] Another function of VGAM859 is therefore inhibition of Zinc Finger Protein 197 (ZNF197, Accession NM\_006991). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF197. LOC115297 (Accession XM\_053313) is another VGAM859 host target gene. LOC115297 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115297, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115297 BINDING SITE, designated SEQ ID:36073, to the nucleotide sequence of

VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32877] Another function of VGAM859 is therefore inhibition of LOC115297 (Accession XM\_053313). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115297. LOC145790 (Accession XM\_085234) is another VGAM859 host target gene. LOC145790 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145790, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145790 BINDING SITE, designated SEQ ID:37980, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32878] Another function of VGAM859 is therefore inhibition of LOC145790 (Accession XM\_085234). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145790. LOC145951 (Accession XM\_085283) is another VGAM859 host target gene. LOC145951 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC145951, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145951 BINDING SITE, designated SEQ ID:38017, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32879] Another function of VGAM859 is therefore inhibition of LOC145951 (Accession XM\_085283). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145951. LOC152220 (Accession XM\_098176) is another VGAM859 host target gene. LOC152220 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152220, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152220 BINDING SITE, designated SEQ ID:41446, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32880] Another function of VGAM859 is therefore inhibition of LOC152220 (Accession XM\_098176). Accordingly, utilities

of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152220. LOC199678 (Accession XM\_117111) is another VGAM859 host target gene. LOC199678 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199678, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199678 BINDING SITE, designated SEQ ID:43228, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32881] Another function of VGAM859 is therefore inhibition of LOC199678 (Accession XM\_117111). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199678. LOC254896 (Accession XM\_171201) is another VGAM859 host target gene. LOC254896 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC254896, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC254896 BINDING SITE, designated SEQ ID:45989, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32882] Another function of VGAM859 is therefore inhibition of LOC254896 (Accession XM\_171201). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254896. LOC257478 (Accession XM\_054745) is another VGAM859 host target gene. LOC257478 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257478, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257478 BINDING SITE, designated SEQ ID:36184, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32883] Another function of VGAM859 is therefore inhibition of LOC257478 (Accession XM\_054745). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257478. LOC57147 (Accession NM\_020423) is another VGAM859 host target gene. LOC57147 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC57147, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57147 BINDING SITE, designated SEQ ID:21681, to the nucleotide sequence of VGAM859 RNA, herein designated VGAM RNA, also designated SEQ ID:3570.

[32884] Another function of VGAM859 is therefore inhibition of LOC57147 (Accession NM\_020423). Accordingly, utilities of VGAM859 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57147. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 860 (VGAM860) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32885] VGAM860 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM860 was detected is described hereinabove with reference to Figs. 1–8.

[32886] VGAM860 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Camelpox Virus.

VGAM860 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32887] VGAM860 gene encodes a VGAM860 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM860 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM860 precursor RNA is designated SEQ ID:846, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:846 is located at position 127064 relative to the genome of Camelpox Virus.

[32888] VGAM860 precursor RNA folds onto itself, forming VGAM860 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-



cleotide sequence of the second half thereof.

[32889] An enzyme complex designated DICER COMPLEX, `dices` the VGAM860 folded precursor RNA into VGAM860 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM860 RNA is designated SEQ ID:3571, and is provided hereinbelow with reference to the sequence listing part.

[32890] VGAM860 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM860 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM860 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32891] VGAM860 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM860 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM860 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM860 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM860 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32892] The complementary binding of VGAM860 RNA, herein designated VGAM RNA, to host target binding sites on VGAM860 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and

BINDING SITE III, inhibits translation of VGAM860 host target RNA into VGAM860 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32893] It is appreciated that VGAM860 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM860 host target genes. The mRNA of each one of this plurality of VGAM860 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM860 RNA, herein designated VGAM RNA, and which when bound by VGAM860 RNA causes inhibition of translation of respective one or more VGAM860 host target proteins.

[32894] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM860 gene, herein designated VGAM GENE, on one or more VGAM860 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32895] It is yet further appreciated that a function of VGAM860 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM860 include diagnosis, prevention and treatment of viral infection by Camelpox Virus. Specific functions, and accordingly utilities, of VGAM860 correlate with, and may be deduced from, the identity of the host target genes which VGAM860 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32896] Nucleotide sequences of the VGAM860 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM860 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM860 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM860 are further described hereinbelow with reference to Table 1.

[32897] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM860 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM860 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32898] As mentioned hereinabove with reference to Fig. 1, a function of VGAM860 gene, herein designated VGAM is inhibition of expression of VGAM860 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM860 correlate with, and may be deduced from, the identity of the target genes which VGAM860 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32899] KIAA0143 (Accession XM\_035825) is a VGAM860 host target gene. KIAA0143 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0143, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0143 BINDING SITE, designated SEQ ID:32351, to the nucleotide sequence of VGAM860 RNA, herein designated VGAM RNA, also designated SEQ ID:3571.

[32900] A function of VGAM860 is therefore inhibition of KIAA0143 (Accession XM\_035825). Accordingly, utilities of VGAM860 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0143. Solute Carrier Family 26, Member 7 (SLC26A7, Accession NM\_052832) is another VGAM860 host target gene. SLC26A7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC26A7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC26A7 BINDING SITE, designated SEQ ID:27417, to the nucleotide sequence of VGAM860 RNA, herein designated VGAM RNA, also designated SEQ ID:3571.

[32901] Another function of VGAM860 is therefore inhibition of Solute Carrier Family 26, Member 7 (SLC26A7, Accession NM\_052832). Accordingly, utilities of VGAM860 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with SLC26A7. LOC158292 (Accession XM\_098914) is another VGAM860 host target gene. LOC158292 BINDING SITE1 and LOC158292 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LOC158292, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158292 BINDING SITE1 and LOC158292 BINDING SITE2, designated SEQ ID:41934 and SEQ ID:41935 respectively, to the nucleotide sequence of VGAM860 RNA, herein designated VGAM RNA, also designated SEQ ID:3571.

[32902] Another function of VGAM860 is therefore inhibition of LOC158292 (Accession XM\_098914). Accordingly, utilities of VGAM860 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158292. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 861 (VGAM861) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[32903] VGAM861 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM861 was detected is described hereinabove with reference to Figs. 1–8.

[32904] VGAM861 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ictalurid Herpesvirus 1. VGAM861 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32905] VGAM861 gene encodes a VGAM861 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM861 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM861 precursor RNA is designated SEQ ID:847, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:847 is located at position 97141 relative to the genome of Ictalurid Herpesvirus 1.

[32906] VGAM861 precursor RNA folds onto itself, forming VGAM861 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional



`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[32907] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM861 folded precursor RNA into VGAM861 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 45%) nucleotide se-  
quence of VGAM861 RNA is designated SEQ ID:3572, and  
is provided hereinbelow with reference to the sequence  
listing part.

[32908] VGAM861 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM861 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM861 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32909] VGAM861 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM861 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM861 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM861 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM861 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[32910] The complementary binding of VGAM861 RNA, herein designated VGAM RNA, to host target binding sites on VGAM861 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM861 host target RNA into VGAM861 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32911] It is appreciated that VGAM861 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM861 host target genes. The mRNA of each one of this plurality of VGAM861 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM861 RNA, herein designated VGAM RNA, and which when bound by VGAM861 RNA causes inhibition of translation of respective one or more VGAM861 host target proteins.

[32912] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM861 gene, herein designated VGAM GENE, on one or

more VGAM861 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32913] It is yet further appreciated that a function of VGAM861 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of viral infection by Ictalurid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM861 correlate with, and may be deduced from, the identity of the host target genes which VGAM861 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [32914] Nucleotide sequences of the VGAM861 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM861 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM861 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM861 are further described hereinbelow with reference to Table 1.
- [32915] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM861 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM861 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [32916] As mentioned hereinabove with reference to Fig. 1, a function of VGAM861 gene, herein designated VGAM is inhibition of expression of VGAM861 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM861 correlate with, and may be deduced from, the identity of the target genes which VGAM861 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [32917] Estrogen-related Receptor Gamma (ESRRG, Accession

XM\_039053) is a VGAM861 host target gene. ESRRG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ESRRG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ESRRG BINDING SITE, designated SEQ ID:33001, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32918] A function of VGAM861 is therefore inhibition of Estrogen-related Receptor Gamma (ESRRG, Accession XM\_039053), a gene which Estrogen-related receptor gamma. Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ESRRG. The function of ESRRG and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM359. Glypican 4 (GPC4, Accession NM\_001448) is another VGAM861 host target gene. GPC4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPC4 BINDING SITE, designated SEQ ID:7179, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32919] Another function of VGAM861 is therefore inhibition of Glypican 4 (GPC4, Accession NM\_001448), a gene which may play a role in growth control and cell division. Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPC4. The function of GPC4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM538. Kinase Insert Domain Receptor (a type III receptor tyrosine kinase) (KDR, Accession NM\_002253) is another VGAM861 host target gene. KDR BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KDR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KDR BINDING SITE, designated SEQ ID:8055, to the nucleotide sequence of VGAM861 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3572.

[32920] Another function of VGAM861 is therefore inhibition of Kinase Insert Domain Receptor (a type III receptor tyrosine kinase) (KDR, Accession NM\_002253). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KDR. Male-specific Lethal 3-like 1 (Drosophila) (MSL3L1, Accession NM\_006800) is another VGAM861 host target gene. MSL3L1 BINDING SITE1 through MSL3L1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by MSL3L1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSL3L1 BINDING SITE1 through MSL3L1 BINDING SITE3, designated SEQ ID:13673, SEQ ID:27813 and SEQ ID:27816 respectively, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32921] Another function of VGAM861 is therefore inhibition of Male-specific Lethal 3-like 1 (Drosophila) (MSL3L1, Accession NM\_006800). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases



and clinical conditions associated with MSL3L1. Sp3 Transcription Factor (SP3, Accession XM\_092672) is another VGAM861 host target gene. SP3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SP3 BINDING SITE, designated SEQ ID:40136, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32922] Another function of VGAM861 is therefore inhibition of Sp3 Transcription Factor (SP3, Accession XM\_092672), a gene which binds to gt and gc boxes promoters elements. Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SP3. The function of SP3 has been established by previous studies. Kingsley and Winoto (1992) noted that in T cells, a consensus GT box similar to the GC box is bound by Sp1. Gel shift analysis showed that other regulatory proteins also bind the GT box. They then cloned 2 novel cDNAs using the Sp1 zinc finger domain as a probe. These new transcription factors, termed Sp2

(OMIM Ref. No. 601801) and Sp3 by them, encode proteins with several transactivation domains and a zinc finger DNA-binding domain with homology to Sp1. The Sp3 cDNA encodes an open reading frame of 713 amino acids. They found that the amino acid sequence of Sp3 is 90% homologous to that of Sp1 within the zinc finger region, and that there is significant homology throughout the protein. Kingsley and Winoto (1992) found that, when expressed in vitro, both Sp1 and Sp3 bind strongly to GC- and GT-box regulatory elements. Hagen et al. (1992) independently performed recognition site screening for factors which bind to the GT motif of the uteroglobin promoter. They isolated Sp3 and Sp4 (OMIM Ref. No. 600540), referring to them as SPR2 and SPR1 (for Sp-related factors 2 and 1) respectively. Northern blot analysis showed that Sp3 is expressed as a 5.0-kb message in all cell lines and tissues tested. Hagen et al. (1994) found that Sp3 represses Sp1-mediated transcriptional activation, suggesting that Sp3 is an inhibitory member of the Sp gene family.

[32923] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [32924] Kalff-Suske, M.; Kunz, J.; Grzeschik, K.-H.; Suske, G. : Human Sp3 transcriptional regulator gene (SP3) maps to chromosome 2q31. *Genomics* 37: 410–412, 1996. ; and
- [32925] Hagen, G.; Muller, S.; Beato, M.; Suske, G. : Cloning by recognition site screening of two novel GT box binding proteins: a family of Sp1 related genes. *Nucleic Acids Res.* 20: 5519–5525, 19.
- [32926] Further studies establishing the function and utilities of SP3 are found in John Hopkins OMIM database record ID 601804, and in cited publications numbered 7689–916 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chromosome 21 Open Reading Frame 25 (C21orf25, Accession XM\_032945) is another VGAM861 host target gene. C21orf25 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C21orf25, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C21orf25 BINDING SITE, designated SEQ ID:31802, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32927] Another function of VGAM861 is therefore inhibition of Chromosome 21 Open Reading Frame 25 (C21orf25, Accession XM\_032945). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C21orf25.

FLJ21106 (Accession NM\_025097) is another VGAM861 host target gene. FLJ21106 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21106 BINDING SITE, designated SEQ ID:24736, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32928] Another function of VGAM861 is therefore inhibition of FLJ21106 (Accession NM\_025097). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21106. KIAA0427 (Accession NM\_014772) is another VGAM861 host target gene. KIAA0427 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0427, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0427 BINDING SITE, designated SEQ ID:16582, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32929] Another function of VGAM861 is therefore inhibition of KIAA0427 (Accession NM\_014772). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0427. Phosphatidylinositol-4-phosphate 5-kinase, Type I, Gamma (PIP5K1C, Accession XM\_047620) is another VGAM861 host target gene. PIP5K1C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIP5K1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIP5K1C BINDING SITE, designated SEQ ID:35019, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32930] Another function of VGAM861 is therefore inhibition of Phosphatidylinositol-4-phosphate 5-kinase, Type I,

Gamma (PIP5K1C, Accession XM\_047620). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP5K1C. Target of Myb1 (chicken) (TOM1, Accession NM\_005488) is another VGAM861 host target gene. TOM1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TOM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOM1 BINDING SITE, designated SEQ ID:11988, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32931] Another function of VGAM861 is therefore inhibition of Target of Myb1 (chicken) (TOM1, Accession NM\_005488). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOM1. LOC116028 (Accession XM\_057225) is another VGAM861 host target gene. LOC116028 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC116028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC116028 BINDING SITE, designated SEQ ID:36494, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32932] Another function of VGAM861 is therefore inhibition of LOC116028 (Accession XM\_057225). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116028. LOC150848 (Accession XM\_097959) is another VGAM861 host target gene. LOC150848 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150848, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150848 BINDING SITE, designated SEQ ID:41260, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32933] Another function of VGAM861 is therefore inhibition of LOC150848 (Accession XM\_097959). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC150848. LOC257471 (Accession XM\_171020) is another VGAM861 host target gene. LOC257471 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257471, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257471 BINDING SITE, designated SEQ ID:45788, to the nucleotide sequence of VGAM861 RNA, herein designated VGAM RNA, also designated SEQ ID:3572.

[32934] Another function of VGAM861 is therefore inhibition of LOC257471 (Accession XM\_171020). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257471. LOC51696 (Accession NM\_016217) is another VGAM861 host target gene. LOC51696 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51696, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51696 BINDING SITE, designated SEQ ID:18318, to the nucleotide sequence of VGAM861 RNA, herein designated



VGAM RNA, also designated SEQ ID:3572.

[32935] Another function of VGAM861 is therefore inhibition of LOC51696 (Accession NM\_016217). Accordingly, utilities of VGAM861 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51696. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 862 (VGAM862) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32936] VGAM862 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM862 was detected is described hereinabove with reference to Figs. 1–8.

[32937] VGAM862 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ictalurid Herpesvirus 1. VGAM862 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32938] VGAM862 gene encodes a VGAM862 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM862 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM862 precursor RNA is designated SEQ ID:848, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:848 is located at position 97256 relative to the genome of Ictalurid Herpesvirus 1.

[32939] VGAM862 precursor RNA folds onto itself, forming VGAM862 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32940] An enzyme complex designated DICER COMPLEX, `dices` the VGAM862 folded precursor RNA into VGAM862 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM862 RNA is designated SEQ ID:3573, and is provided hereinbelow with reference to the sequence listing part.

[32941] VGAM862 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM862 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM862 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[32942] VGAM862 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM862 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM862 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM862 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM862 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[32943] The complementary binding of VGAM862 RNA, herein designated VGAM RNA, to host target binding sites on VGAM862 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM862 host target RNA into VGAM862 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32944] It is appreciated that VGAM862 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM862 host target genes. The mRNA of

each one of this plurality of VGAM862 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM862 RNA, herein designated VGAM RNA, and which when bound by VGAM862 RNA causes inhibition of translation of respective one or more VGAM862 host target proteins.

[32945] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM862 gene, herein designated VGAM GENE, on one or more VGAM862 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[32946] It is yet further appreciated that a function of VGAM862 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of viral infection by Ictalurid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM862 correlate with, and may be deduced from, the identity of the host target genes which VGAM862 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32947] Nucleotide sequences of the VGAM862 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM862 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM862 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM862 are further described hereinbelow with reference to Table 1.

[32948] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM862 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM862 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[32949] As mentioned hereinabove with reference to Fig. 1, a function of VGAM862 gene, herein designated VGAM is inhibition of expression of VGAM862 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM862 correlate with, and may be deduced from, the identity of the target genes which VGAM862 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32950] BLTR2 (Accession NM\_019839) is a VGAM862 host target gene. BLTR2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BLTR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BLTR2 BINDING SITE, designated SEQ ID:21242, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32951] A function of VGAM862 is therefore inhibition of BLTR2 (Accession NM\_019839). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with BLTR2. Dishevelled, Dsh Homolog 3 (Drosophila) (DVL3, Accession NM\_004423) is another VGAM862 host target gene. DVL3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DVL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DVL3 BINDING SITE, designated SEQ ID:10691, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32952] Another function of VGAM862 is therefore inhibition of Dishevelled, Dsh Homolog 3 (Drosophila) (DVL3, Accession NM\_004423), a gene which regulates cell proliferation. Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DVL3. The function of DVL3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM57. Fibroblast Growth Factor 5 (FGF5, Accession NM\_004464) is another VGAM862 host target gene. FGF5 BINDING SITE1 and FGF5 BINDING SITE2 are HOST TARGET binding sites found in



untranslated regions of mRNA encoded by FGF5, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF5 BINDING SITE1 and FGF5 BINDING SITE2, designated SEQ ID:10772 and SEQ ID:26999 respectively, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32953] Another function of VGAM862 is therefore inhibition of Fibroblast Growth Factor 5 (FGF5, Accession NM\_004464), a gene which induces transformation and may regulate neuronal differentiation. Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF5. The function of FGF5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM276. Solute Carrier Family 8 (sodium-calcium exchanger), Member 2 (SLC8A2, Accession XM\_038970) is another VGAM862 host target gene. SLC8A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC8A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC8A2 BINDING SITE, designated SEQ ID:32966, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32954] Another function of VGAM862 is therefore inhibition of Solute Carrier Family 8 (sodium–calcium exchanger), Member 2 (SLC8A2, Accession XM\_038970). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC8A2. Small Optic Lobes Homolog (*Drosophila*) (SOLH, Accession NM\_005632) is another VGAM862 host target gene. SOLH BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SOLH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOLH BINDING SITE, designated SEQ ID:12163, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32955] Another function of VGAM862 is therefore inhibition of Small Optic Lobes Homolog (*Drosophila*) (SOLH, Accession

NM\_005632), a gene which has several domains (calpain-like domain, zinc fingers) and homologous to the *Drosophila sol*. Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOLH. The function of SOLH has been established by previous studies. The *Drosophila* small optic lobes (*sol*) gene encodes a protein with zinc finger-like repeats, a calpain (see OMIM Ref. No. 114240)-like protease domain, and a C-terminal region of unknown function. Mutations in *sol* cause a severe reduction in the cell numbers of the neuropiles of the medulla and lobula complexes of the adult optic lobes. Banfi et al. (1996) identified a human EST encoding a protein with homology to the *sol* gene product. By screening human brain cDNA libraries with this EST, Kamei et al. (1998) isolated cDNAs corresponding to the complete coding sequence of SOLH. The predicted 1,086-amino acid protein shares 44% sequence identity with *sol*. The calpain-like domain and C-terminal region are highly conserved between SOLH and *sol*, and similar zinc fingers are present in the N-terminal regions of these proteins. The SOLH gene contains at least 14 exons distributed over more than 45 kb. Southern blot analysis indicated that SOLH is a

single-copy gene. Using Northern blots, the authors demonstrated that SOLH is expressed as an approximately 5-kb mRNA in various human tissues; additional smaller transcripts were observed in some tissues. Kamei et al. (1998) identified cDNAs and genomic clones encoding mouse, *C. elegans*, and *Fugu rubripes* (Japanese pufferfish) homologs of sol.

[32956] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[32957] Banfi, S.; Borsani, G.; Rossi, E.; Bernard, L.; Guffanti, A.; Rubboli, F.; Marchitello, A.; Giglio, S.; Coluccia, E.; Zollo, M.; Zuffardi, O.; Ballabio, A. : Identification and mapping of human cDNAs homologous to *Drosophila* mutant genes through EST database searching. *Nature Genet.* 13: 167–174, 1996. ; and

[32958] Kamei, M.; Webb, G. C.; Young, I. G.; Campbell, H. D. : SOLH, a human homologue of the *Drosophila melanogaster* small optic lobes gene is a member of the calpain and zinc-finger gene famili.

[32959] Further studies establishing the function and utilities of SOLH are found in John Hopkins OMIM database record ID 603267, and in sited publications numbered 602 and

6331 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ12816 (Accession NM\_022060) is another VGAM862 host target gene. FLJ12816 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12816, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12816 BINDING SITE, designated SEQ ID:22602, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32960] Another function of VGAM862 is therefore inhibition of FLJ12816 (Accession NM\_022060). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12816. FLJ22471 (Accession NM\_025140) is another VGAM862 host target gene. FLJ22471 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22471, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22471 BINDING SITE,

designated SEQ ID:24777, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32961] Another function of VGAM862 is therefore inhibition of FLJ22471 (Accession NM\_025140). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22471. KIAA1322 (Accession XM\_052626) is another VGAM862 host target gene. KIAA1322 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1322 BINDING SITE, designated SEQ ID:36020, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32962] Another function of VGAM862 is therefore inhibition of KIAA1322 (Accession XM\_052626). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1322. PRO0097 (Accession NM\_014114) is another VGAM862 host target gene. PRO0097 BINDING SITE is

HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO0097, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0097 BINDING SITE, designated SEQ ID:15364, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32963] Another function of VGAM862 is therefore inhibition of PRO0097 (Accession NM\_014114). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0097. ZFP106 (Accession NM\_022473) is another VGAM862 host target gene. ZFP106 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ZFP106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFP106 BINDING SITE, designated SEQ ID:22829, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32964] Another function of VGAM862 is therefore inhibition of

ZFP106 (Accession NM\_022473). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFP106. LOC150397 (Accession XM\_086907) is another VGAM862 host target gene. LOC150397 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150397 BINDING SITE, designated SEQ ID:38959, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32965] Another function of VGAM862 is therefore inhibition of LOC150397 (Accession XM\_086907). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150397. LOC163682 (Accession XM\_099402) is another VGAM862 host target gene. LOC163682 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163682, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-



illustrates the complementarity of the nucleotide sequences of LOC163682 BINDING SITE, designated SEQ ID:42086, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32966] Another function of VGAM862 is therefore inhibition of LOC163682 (Accession XM\_099402). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163682. LOC222171 (Accession XM\_166586) is another VGAM862 host target gene. LOC222171 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC222171, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222171 BINDING SITE, designated SEQ ID:44558, to the nucleotide sequence of VGAM862 RNA, herein designated VGAM RNA, also designated SEQ ID:3573.

[32967] Another function of VGAM862 is therefore inhibition of LOC222171 (Accession XM\_166586). Accordingly, utilities of VGAM862 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222171. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 863 (VGAM863) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32968] VGAM863 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM863 was detected is described hereinabove with reference to Figs. 1–8.

[32969] VGAM863 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ictalurid Herpesvirus 1. VGAM863 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32970] VGAM863 gene encodes a VGAM863 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM863 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM863 precursor RNA is designated SEQ ID:849, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:849 is

located at position 99448 relative to the genome of Ictalurid Herpesvirus 1.

[32971] VGAM863 precursor RNA folds onto itself, forming VGAM863 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32972] An enzyme complex designated DICER COMPLEX, `dices` the VGAM863 folded precursor RNA into VGAM863 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM863 RNA is designated SEQ ID:3574, and is provided hereinbelow with reference to the sequence listing part.

[32973] VGAM863 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM863 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM863 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[32974] VGAM863 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM863 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM863 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM863 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM863 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[32975] The complementary binding of VGAM863 RNA, herein designated VGAM RNA, to host target binding sites on VGAM863 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM863 host target RNA into VGAM863 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[32976] It is appreciated that VGAM863 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM863 host target genes. The mRNA of each one of this plurality of VGAM863 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM863 RNA, herein designated VGAM RNA, and which when bound by VGAM863 RNA causes inhibition of translation of respective one or more VGAM863

host target proteins.

[32977] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM863 gene, herein designated VGAM GENE, on one or more VGAM863 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[32978] It is yet further appreciated that a function of VGAM863 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of viral infection by Ictalurid Herpesvirus 1.

Specific functions, and accordingly utilities, of VGAM863 correlate with, and may be deduced from, the identity of the host target genes which VGAM863 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[32979] Nucleotide sequences of the VGAM863 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM863 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM863 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM863 are further described hereinbelow with reference to Table 1.

[32980] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM863 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM863 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[32981] As mentioned hereinabove with reference to Fig. 1, a function of VGAM863 gene, herein designated VGAM is inhibition of expression of VGAM863 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM863 correlate with, and may be deduced from, the identity of the target genes which VGAM863 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[32982] Axin 1 (AXIN1, Accession XM\_027520) is a VGAM863 host target gene. AXIN1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AXIN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AXIN1 BINDING SITE, designated SEQ ID:30513, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32983] A function of VGAM863 is therefore inhibition of Axin 1 (AXIN1, Accession XM\_027520). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AXIN1. Lysosomal-associated Membrane Protein 2 (LAMP2, Accession NM\_013995) is another VGAM863 host target gene. LAMP2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LAMP2, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LAMP2 BINDING SITE, designated SEQ ID:15182, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32984] Another function of VGAM863 is therefore inhibition of Lysosomal-associated Membrane Protein 2 (LAMP2, Accession NM\_013995). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LAMP2. Lymphotoxin Alpha (TNF superfamily, member 1) (LTA, Accession NM\_000595) is another VGAM863 host target gene. LTA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LTA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LTA BINDING SITE, designated SEQ ID:6193, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32985] Another function of VGAM863 is therefore inhibition of Lymphotoxin Alpha (TNF superfamily, member 1) (LTA,

Accession NM\_000595), a gene which is a cytokine that in its homotrimeric form binds to tnfrsf1a/tnfr1, tnfrsf1b/tnfr and tnfrsf14/hvem. Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LTA. The function of LTA and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM662. ATP-binding Cassette, Sub-family A (ABC1), Member 9 (ABCA9, Accession NM\_080283) is another VGAM863 host target gene. ABCA9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABCA9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABCA9 BINDING SITE, designated SEQ ID:27826, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32986] Another function of VGAM863 is therefore inhibition of ATP-binding Cassette, Sub-family A (ABC1), Member 9 (ABCA9, Accession NM\_080283). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with ABCA9. FASTK (Accession NM\_025096) is another VGAM863 host target gene. FASTK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FASTK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FASTK BINDING SITE, designated SEQ ID:24726, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32987] Another function of VGAM863 is therefore inhibition of FASTK (Accession NM\_025096). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FASTK. FLJ14437 (Accession NM\_032578) is another VGAM863 host target gene. FLJ14437 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14437, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14437 BINDING SITE, designated SEQ ID:26306, to the nucleotide sequence of

VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32988] Another function of VGAM863 is therefore inhibition of FLJ14437 (Accession NM\_032578). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14437. KIAA0125 (Accession XM\_018203) is another VGAM863 host target gene. KIAA0125 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0125, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0125 BINDING SITE, designated SEQ ID:30344, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32989] Another function of VGAM863 is therefore inhibition of KIAA0125 (Accession XM\_018203). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0125. KIAA1505 (Accession XM\_168469) is another VGAM863 host target gene. KIAA1505 BINDING SITE is HOST TARGET binding site found in the 5' untranslated

region of mRNA encoded by KIAA1505, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1505 BINDING SITE, designated SEQ ID:45191, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32990] Another function of VGAM863 is therefore inhibition of KIAA1505 (Accession XM\_168469). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1505. MGC39436 (Accession NM\_144673) is another VGAM863 host target gene. MGC39436 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC39436, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC39436 BINDING SITE, designated SEQ ID:29495, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32991] Another function of VGAM863 is therefore inhibition of MGC39436 (Accession NM\_144673). Accordingly, utilities

of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC39436. NYD-SP27 (Accession NM\_033123) is another VGAM863 host target gene. NYD-SP27 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by NYD-SP27, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP27 BINDING SITE, designated SEQ ID:26967, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32992] Another function of VGAM863 is therefore inhibition of NYD-SP27 (Accession NM\_033123). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP27. Suppression of Tumorigenicity 7 Like (ST7L, Accession NM\_139195) is another VGAM863 host target gene. ST7L BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ST7L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide se-

quences of ST7L BINDING SITE, designated SEQ ID:29203, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32993] Another function of VGAM863 is therefore inhibition of Suppression of Tumorigenicity 7 Like (ST7L, Accession NM\_139195). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ST7L. LOC158434 (Accession XM\_098939) is another VGAM863 host target gene. LOC158434 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC158434, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158434 BINDING SITE, designated SEQ ID:41981, to the nucleotide sequence of VGAM863 RNA, herein designated VGAM RNA, also designated SEQ ID:3574.

[32994] Another function of VGAM863 is therefore inhibition of LOC158434 (Accession XM\_098939). Accordingly, utilities of VGAM863 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158434. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 864 (VGAM864) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[32995] VGAM864 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM864 was detected is described hereinabove with reference to Figs. 1–8.

[32996] VGAM864 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Ictalurid Herpesvirus 1. VGAM864 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[32997] VGAM864 gene encodes a VGAM864 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM864 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM864 precursor RNA is designated SEQ ID:850, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:850 is



located at position 96883 relative to the genome of Ictalurid Herpesvirus 1.

[32998] VGAM864 precursor RNA folds onto itself, forming VGAM864 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[32999] An enzyme complex designated DICER COMPLEX, `dices` the VGAM864 folded precursor RNA into VGAM864 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM864 RNA is designated SEQ ID:3575, and is provided hereinbelow with reference to the sequence listing part.

[33000] VGAM864 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM864 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM864 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33001] VGAM864 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM864 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM864 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM864 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM864 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[33002] The complementary binding of VGAM864 RNA, herein designated VGAM RNA, to host target binding sites on VGAM864 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM864 host target RNA into VGAM864 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33003] It is appreciated that VGAM864 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM864 host target genes. The mRNA of each one of this plurality of VGAM864 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM864 RNA, herein designated VGAM RNA, and which when bound by VGAM864 RNA causes inhibition of translation of respective one or more VGAM864

host target proteins.

[33004] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM864 gene, herein designated VGAM GENE, on one or more VGAM864 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33005] It is yet further appreciated that a function of VGAM864 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM864 include diagnosis, prevention and treatment of viral infection by Ictalurid Herpesvirus 1.

Specific functions, and accordingly utilities, of VGAM864 correlate with, and may be deduced from, the identity of the host target genes which VGAM864 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [33006] Nucleotide sequences of the VGAM864 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM864 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM864 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM864 are further described hereinbelow with reference to Table 1.
- [33007] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM864 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM864 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33008] As mentioned hereinabove with reference to Fig. 1, a function of VGAM864 gene, herein designated VGAM is inhibition of expression of VGAM864 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM864 correlate with, and may be deduced from, the identity of the target genes which VGAM864 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33009] Fibroblast Growth Factor 9 (glia-activating factor) (FGF9, Accession NM\_002010) is a VGAM864 host target gene. FGF9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FGF9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF9 BINDING SITE, designated SEQ ID:7751, to the nucleotide sequence of VGAM864 RNA, herein designated VGAM RNA, also designated SEQ ID:3575.

[33010] A function of VGAM864 is therefore inhibition of Fibroblast Growth Factor 9 (glia-activating factor) (FGF9, Accession NM\_002010), a gene which Fibroblast growth factor 9 (glia-activating factor); secreted mitogen. Accordingly, utilities of VGAM864 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF9. The function of FGF9 has been established by previous studies. Members of the fibroblast growth factor (FGF) gene family (e.g., FGF1; 131220) are peptide regula-

tory factors acting through 4 distinct tyrosine kinase receptors and involved in various biologic processes during embryogenesis and adult life, including implantation, morphogenesis, angiogenesis, and possibly tumorigenesis. Miyamoto et al. (1993) cloned the ninth member of the FGF family. By radioactive chromosomal in situ hybridization, Mattei et al. (1995) mapped the gene to 13q11-q12. Using the Cre/loxP system, Sun et al. (2000) found that maintenance of Fgf9 and Fgf17 (OMIM Ref. No. 603725) expression is dependent on Shh (OMIM Ref. No. 600725), whereas Fgf8 (OMIM Ref. No. 600483) expression is not. Sun et al. (2000) developed a model in which no individual Fgf expressed in the apical ectodermal ridge is solely necessary to maintain Shh expression, but instead the combined activity of 2 or more apical ectodermal ridge Fgfs function in a positive feedback loop with Shh to control limb development. Colvin et al. (2001) reported male-to-female sex reversal in mice lacking Fgf9, demonstrating a novel role for FGF signaling in testicular embryogenesis. Fgf9  $-/-$  mice also exhibited lung hypoplasia and died at birth. Reproductive system phenotypes ranged from testicular hypoplasia to complete sex reversal, with most Fgf9  $-/-$  XY reproductive systems ap-

pearing grossly female at birth. Fgf9 appeared to act downstream of Sry (OMIM Ref. No. 480000) to stimulate mesenchymal proliferation, mesonephric cell migration, and Sertoli cell differentiation in the embryonic testis.

While Sry is found only in some mammals, Fgfs are highly conserved. Thus, Fgfs may function in sex determination and reproductive system development in many species.

[33011] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33012] Colvin, J. S.; Green, R. P.; Schmahl, J.; Capel, B.; Ornitz, D. M. : Male-to-female sex reversal in mice lacking fibroblast growth factor 9. Cell 104: 875–889, 2001. ; and

[33013] Sun, X.; Lewandoski, M.; Meyers, E. N.; Liu, Y.-H.; Maxson, R. E., Jr.; Martin, G. R. : Conditional inactivation of Fgf4 reveals complexity of signalling during limb bud development. Na.

[33014] Further studies establishing the function and utilities of FGF9 are found in John Hopkins OMIM database record ID 600921, and in cited publications numbered 9955–995 and 3289 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Guanylate Binding Protein 1, Interferon-inducible, 67kDa (GBP1, Ac-



cession NM\_002053) is another VGAM864 host target gene. GBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GBP1 BINDING SITE, designated SEQ ID:7809, to the nucleotide sequence of VGAM864 RNA, herein designated VGAM RNA, also designated SEQ ID:3575.

[33015] Another function of VGAM864 is therefore inhibition of Guanylate Binding Protein 1, Interferon-inducible, 67kDa (GBP1, Accession NM\_002053), a gene which specifically binds guanylate nucleotides (GMP, GDP and GTP). Accordingly, utilities of VGAM864 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GBP1. The function of GBP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM46. GEMIN5 (Accession XM\_114471) is another VGAM864 host target gene. GEMIN5 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GEMIN5, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GEMIN5 BINDING SITE, designated SEQ ID:42974, to the nucleotide sequence of VGAM864 RNA, herein designated VGAM RNA, also designated SEQ ID:3575.

[33016] Another function of VGAM864 is therefore inhibition of GEMIN5 (Accession XM\_114471). Accordingly, utilities of VGAM864 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GEMIN5. DKFZp434D177 (Accession NM\_032264) is another VGAM864 host target gene. DKFZp434D177 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZp434D177, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434D177 BINDING SITE, designated SEQ ID:26009, to the nucleotide sequence of VGAM864 RNA, herein designated VGAM RNA, also designated SEQ ID:3575.

[33017] Another function of VGAM864 is therefore inhibition of DKFZp434D177 (Accession NM\_032264). Accordingly, utilities of VGAM864 include diagnosis, prevention and

treatment of diseases and clinical conditions associated with DKFZp434D177. LOC123745 (Accession XM\_063826) is another VGAM864 host target gene. LOC123745 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC123745, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC123745 BINDING SITE, designated SEQ ID:37255, to the nucleotide sequence of VGAM864 RNA, herein designated VGAM RNA, also designated SEQ ID:3575.

[33018] Another function of VGAM864 is therefore inhibition of LOC123745 (Accession XM\_063826). Accordingly, utilities of VGAM864 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC123745. LOC149010 (Accession XM\_086397) is another VGAM864 host target gene. LOC149010 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149010, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149010 BINDING SITE, designated SEQ ID:38629, to

the nucleotide sequence of VGAM864 RNA, herein designated VGAM RNA, also designated SEQ ID:3575.

[33019] Another function of VGAM864 is therefore inhibition of LOC149010 (Accession XM\_086397). Accordingly, utilities of VGAM864 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149010. LOC162333 (Accession XM\_102591) is another VGAM864 host target gene. LOC162333 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC162333, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC162333 BINDING SITE, designated SEQ ID:42143, to the nucleotide sequence of VGAM864 RNA, herein designated VGAM RNA, also designated SEQ ID:3575.

[33020] Another function of VGAM864 is therefore inhibition of LOC162333 (Accession XM\_102591). Accordingly, utilities of VGAM864 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC162333. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 865 (VGAM865) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33021] VGAM865 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM865 was detected is described hereinabove with reference to Figs. 1–8.

[33022] VGAM865 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Swinepox Virus. VGAM865 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33023] VGAM865 gene encodes a VGAM865 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM865 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM865 precursor RNA is designated SEQ ID:851, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:851 is located at position 38140 relative to the genome of Swinepox Virus.

[33024] VGAM865 precursor RNA folds onto itself, forming VGAM865 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33025] An enzyme complex designated DICER COMPLEX, `dices` the VGAM865 folded precursor RNA into VGAM865 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM865 RNA is designated SEQ ID:3576, and is provided hereinbelow with reference to the sequence listing part.

[33026] VGAM865 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM865 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM865 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33027] VGAM865 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM865 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM865 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM865 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM865 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33028] The complementary binding of VGAM865 RNA, herein designated VGAM RNA, to host target binding sites on VGAM865 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM865 host target RNA into VGAM865 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33029] It is appreciated that VGAM865 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM865 host target genes. The mRNA of each one of this plurality of VGAM865 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM865 RNA, herein designated VGAM RNA, and which when bound by VGAM865 RNA causes inhibition of translation of respective one or more VGAM865 host target proteins.

[33030] It is further appreciated by one skilled in the art that the



mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM865 gene, herein designated VGAM GENE, on one or more VGAM865 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33031] It is yet further appreciated that a function of VGAM865 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of viral infection by Swinepox Virus. Specific functions, and accordingly utilities, of VGAM865 correlate with, and may be deduced from, the identity of the host

target genes which VGAM865 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [33032] Nucleotide sequences of the VGAM865 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM865 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM865 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM865 are further described hereinbelow with reference to Table 1.
- [33033] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM865 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM865 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33034] As mentioned hereinabove with reference to Fig. 1, a function of VGAM865 gene, herein designated VGAM is inhibition of expression of VGAM865 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM865 correlate with, and may be deduced from, the identity of the target genes which VGAM865

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33035] LNK (Accession NM\_005475) is a VGAM865 host target gene. LNK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LNK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LNK BINDING SITE, designated SEQ ID:11968, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33036] A function of VGAM865 is therefore inhibition of LNK (Accession NM\_005475), a gene which links T-cell receptor activation signal to phospholipase c-gamma-1, grb-2 and phosphatidylinositol 3-kinase (by similarity). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LNK. The function of LNK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM115. Reticulocalbin 1, EF-hand Calcium Binding Domain (RCN1, Accession NM\_002901) is another VGAM865 host target gene. RCN1 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RCN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RCN1 BINDING SITE, designated SEQ ID:8803, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33037] Another function of VGAM865 is therefore inhibition of Reticulocalbin 1, EF-hand Calcium Binding Domain (RCN1, Accession NM\_002901), a gene which may regulate calcium-dependent activities in the ER lumen or post-ER compartment. Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RCN1. The function of RCN1 has been established by previous studies. The endoplasmic reticulum (ER) is the major storage compartment for calcium in most eukaryotic cells. Ozawa and Muramatsu (1993) identified cDNAs encoding mouse reticulocalbin (Rcn), a calcium-binding protein located in the lumen of the ER. By PCR using oligonucleotides based on the nucleotide sequence of mouse Rcn, Ozawa (1995) isolated cDNAs encoding RCN1 from human transitional car-

cinoma cell line cDNAs. The predicted 331-amino acid human RCN1 protein is 95% identical to the mouse Rcn protein. RCN1 contains a leader peptide, 6 EF-hand calcium-binding motifs, and a C-terminal HDEL sequence, which serves as an ER retention signal. By Western blot analysis of human mammalian cell extracts, antibodies against Rcn recognized 44- and 46-kD proteins. Northern blot analysis revealed that RCN1 was expressed as a 2.4-kb transcript in all tissues tested. Kent et al. (1997) identified the human RCN1 gene within a cosmid contig of 11p13 and localized it between the WT1 (OMIM Ref. No. 607102) and PAX6 (OMIM Ref. No. 607108) genes. By interspecific backcross analysis, Kent et al. (1997) mapped the mouse Rcn gene to chromosome 2, in a region showing homology of synteny with human 11p14-p13.

[33038] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33039] Ozawa, M. : Cloning of a human homologue of mouse reticulocalbin reveals conservation of structural domains in the novel endoplasmic reticulum resident  $\text{Ca}^{2+}$ -binding protein with multiple EF-hand motifs. J. Biochem. 117: 1113-1119, 1995. ; and

[33040] Kent, J.; Lee, M.; Schedl, A.; Boyle, S.; Fantes, J.; Powell, M.; Rushmere, N.; Abbott, C.; van Heyningen, V.; Bickmore, W. A. : The reticulocalbin gene maps to the WAGR region in human.

[33041] Further studies establishing the function and utilities of RCN1 are found in John Hopkins OMIM database record ID 602735, and in cited publications numbered 8765–8767 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. FLJ22795 (Accession NM\_025084) is another VGAM865 host target gene. FLJ22795 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22795, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22795 BINDING SITE, designated SEQ ID:24688, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33042] Another function of VGAM865 is therefore inhibition of FLJ22795 (Accession NM\_025084). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22795.

TNF Receptor-associated Factor 6 (TRAF6, Accession NM\_004620) is another VGAM865 host target gene. TRAF6 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by TRAF6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRAF6 BINDING SITE, designated SEQ ID:10969, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33043] Another function of VGAM865 is therefore inhibition of TNF Receptor-associated Factor 6 (TRAF6, Accession NM\_004620). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRAF6. LOC121599 (Accession XM\_058576) is another VGAM865 host target gene. LOC121599 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC121599, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC121599 BINDING SITE, desig-

nated SEQ ID:36672, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33044] Another function of VGAM865 is therefore inhibition of LOC121599 (Accession XM\_058576). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC121599. LOC145717 (Accession XM\_039771) is another VGAM865 host target gene. LOC145717 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145717, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145717 BINDING SITE, designated SEQ ID:33189, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33045] Another function of VGAM865 is therefore inhibition of LOC145717 (Accession XM\_039771). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145717. LOC220537 (Accession XM\_165406) is another VGAM865 host target gene. LOC220537 BINDING



SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC220537, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220537 BINDING SITE, designated SEQ ID:43621, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33046] Another function of VGAM865 is therefore inhibition of LOC220537 (Accession XM\_165406). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220537. LOC51580 (Accession NM\_015874) is another VGAM865 host target gene. LOC51580 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC51580, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51580 BINDING SITE, designated SEQ ID:18010, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33047] Another function of VGAM865 is therefore inhibition of

LOC51580 (Accession NM\_015874). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51580. LOC54103 (Accession XM\_168508) is another VGAM865 host target gene. LOC54103 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC54103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC54103 BINDING SITE, designated SEQ ID:45209, to the nucleotide sequence of VGAM865 RNA, herein designated VGAM RNA, also designated SEQ ID:3576.

[33048] Another function of VGAM865 is therefore inhibition of LOC54103 (Accession XM\_168508). Accordingly, utilities of VGAM865 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC54103. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 866 (VGAM866) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[33049] VGAM866 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM866 was detected is described hereinabove with reference to Figs. 1–8.

[33050] VGAM866 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Swinepox Virus. VGAM866 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33051] VGAM866 gene encodes a VGAM866 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM866 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM866 precursor RNA is designated SEQ ID:852, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:852 is located at position 37456 relative to the genome of Swinepox Virus.

[33052] VGAM866 precursor RNA folds onto itself, forming VGAM866 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[33053] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM866 folded precursor RNA into VGAM866 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM866 RNA is designated SEQ ID:3577, and  
is provided hereinbelow with reference to the sequence  
listing part.

[33054] VGAM866 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM866 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM866 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33055] VGAM866 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM866 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM866 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM866 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM866 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[33056] The complementary binding of VGAM866 RNA, herein designated VGAM RNA, to host target binding sites on VGAM866 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM866 host target RNA into VGAM866 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33057] It is appreciated that VGAM866 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM866 host target genes. The mRNA of each one of this plurality of VGAM866 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM866 RNA, herein designated VGAM RNA, and which when bound by VGAM866 RNA causes inhibition of translation of respective one or more VGAM866 host target proteins.

[33058] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM866 gene, herein designated VGAM GENE, on one or

more VGAM866 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33059] It is yet further appreciated that a function of VGAM866 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM866 include diagnosis, prevention and treatment of viral infection by Swinepox Virus. Specific functions, and accordingly utilities, of VGAM866 correlate with, and may be deduced from, the identity of the host target genes which VGAM866 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [33060] Nucleotide sequences of the VGAM866 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM866 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM866 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM866 are further described hereinbelow with reference to Table 1.
- [33061] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM866 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM866 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33062] As mentioned hereinabove with reference to Fig. 1, a function of VGAM866 gene, herein designated VGAM is inhibition of expression of VGAM866 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM866 correlate with, and may be deduced from, the identity of the target genes which VGAM866 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [33063] Kinesin Family Member 5C (KIF5C, Accession NM\_004522)



is a VGAM866 host target gene. KIF5C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIF5C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIF5C BINDING SITE, designated SEQ ID:10856, to the nucleotide sequence of VGAM866 RNA, herein designated VGAM RNA, also designated SEQ ID:3577.

[33064] A function of VGAM866 is therefore inhibition of Kinesin Family Member 5C (KIF5C, Accession NM\_004522). Accordingly, utilities of VGAM866 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIF5C. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 867 (VGAM867) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33065] VGAM867 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM867 was detected is described

hereinabove with reference to Figs. 1–8.

[33066] VGAM867 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turkey Adenovirus 3.

VGAM867 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33067] VGAM867 gene encodes a VGAM867 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM867 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM867 precursor RNA is designated SEQ ID:853, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:853 is located at position 5962 relative to the genome of Turkey Adenovirus 3.

[33068] VGAM867 precursor RNA folds onto itself, forming VGAM867 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33069] An enzyme complex designated DICER COMPLEX, `dices` the VGAM867 folded precursor RNA into VGAM867 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM867 RNA is designated SEQ ID:3578, and is provided hereinbelow with reference to the sequence listing part.

[33070] VGAM867 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM867 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM867 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33071] VGAM867 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM867 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM867 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM867 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM867 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33072] The complementary binding of VGAM867 RNA, herein designated VGAM RNA, to host target binding sites on VGAM867 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM867 host target RNA into VGAM867 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33073] It is appreciated that VGAM867 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM867 host target genes. The mRNA of each one of this plurality of VGAM867 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM867 RNA, herein designated VGAM RNA, and which when bound by VGAM867 RNA causes inhibition of translation of respective one or more VGAM867 host target proteins.

[33074] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM867 gene, herein designated VGAM GENE, on one or more VGAM867 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33075] It is yet further appreciated that a function of VGAM867 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM867 include diagnosis, prevention and treatment of viral infection by Turkey Adenovirus 3. Specific functions, and accordingly utilities, of VGAM867 correlate with, and may be deduced from, the identity of the host target genes which VGAM867 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33076] Nucleotide sequences of the VGAM867 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM867 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM867 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM867 are further described hereinbelow with reference to Table 1.

[33077] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM867 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM867 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33078] As mentioned hereinabove with reference to Fig. 1, a function of VGAM867 gene, herein designated VGAM is inhibition of expression of VGAM867 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM867 correlate with, and may be deduced from, the identity of the target genes which VGAM867 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33079] CAP350 (Accession NM\_014810) is a VGAM867 host target gene. CAP350 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CAP350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of CAP350 BINDING SITE, designated SEQ ID:16768, to the nucleotide sequence of VGAM867 RNA, herein designated VGAM RNA, also designated SEQ ID:3578.

[33080] A function of VGAM867 is therefore inhibition of CAP350 (Accession NM\_014810). Accordingly, utilities of VGAM867 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAP350. LOC219942 (Accession XM\_167790) is another VGAM867 host target gene. LOC219942 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219942, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219942 BINDING SITE, designated SEQ ID:44827, to the nucleotide sequence of VGAM867 RNA, herein designated VGAM RNA, also designated SEQ ID:3578.

[33081] Another function of VGAM867 is therefore inhibition of LOC219942 (Accession XM\_167790). Accordingly, utilities of VGAM867 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC219942. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 868 (VGAM868) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33082] VGAM868 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM868 was detected is described hereinabove with reference to Figs. 1–8.

[33083] VGAM868 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Turkey Adenovirus 3. VGAM868 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33084] VGAM868 gene encodes a VGAM868 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM868 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM868 precursor RNA is designated SEQ ID:854, and is provided hereinbelow with reference to the

sequence listing part. Nucleotide sequence SEQ ID:854 is located at position 5577 relative to the genome of Turkey Adenovirus 3.

[33085] VGAM868 precursor RNA folds onto itself, forming VGAM868 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33086] An enzyme complex designated DICER COMPLEX, `dices` the VGAM868 folded precursor RNA into VGAM868 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM868 RNA is designated SEQ ID:3579, and is provided hereinbelow with reference to the sequence listing part.

[33087] VGAM868 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM868 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM868 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33088] VGAM868 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM868 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM868 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM868 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM868 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[33089] The complementary binding of VGAM868 RNA, herein designated VGAM RNA, to host target binding sites on VGAM868 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM868 host target RNA into VGAM868 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33090] It is appreciated that VGAM868 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM868 host target genes. The mRNA of each one of this plurality of VGAM868 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM868 RNA, herein designated VGAM RNA, and which when bound by VGAM868 RNA causes in-

hibition of translation of respective one or more VGAM868 host target proteins.

[33091] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM868 gene, herein designated VGAM GENE, on one or more VGAM868 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33092] It is yet further appreciated that a function of VGAM868 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM868 include diagnosis, prevention and

treatment of viral infection by Turkey Adenovirus 3. Specific functions, and accordingly utilities, of VGAM868 correlate with, and may be deduced from, the identity of the host target genes which VGAM868 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [33093] Nucleotide sequences of the VGAM868 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM868 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM868 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM868 are further described hereinbelow with reference to Table 1.
- [33094] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM868 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM868 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33095] As mentioned hereinabove with reference to Fig. 1, a function of VGAM868 gene, herein designated VGAM is inhibition of expression of VGAM868 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM868 correlate with, and may be deduced from, the identity of the target genes which VGAM868 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33096] Matrilin 3 (MATN3, Accession NM\_002381) is a VGAM868 host target gene. MATN3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MATN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MATN3 BINDING SITE, designated SEQ ID:8197, to the nucleotide sequence of VGAM868 RNA, herein designated VGAM RNA, also designated SEQ ID:3579.

[33097] A function of VGAM868 is therefore inhibition of Matrilin 3 (MATN3, Accession NM\_002381). Accordingly, utilities of VGAM868 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MATN3. AAK1 (Accession NM\_014911) is another VGAM868 host target gene. AAK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AAK1, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AAK1 BINDING SITE, designated SEQ ID:17144, to the nucleotide sequence of VGAM868 RNA, herein designated VGAM RNA, also designated SEQ ID:3579.

[33098] Another function of VGAM868 is therefore inhibition of AAK1 (Accession NM\_014911). Accordingly, utilities of VGAM868 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AAK1. DKFZP434A043 (Accession NM\_015396) is another VGAM868 host target gene. DKFZP434A043 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434A043, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434A043 BINDING SITE, designated SEQ ID:17703, to the nucleotide sequence of VGAM868 RNA, herein designated VGAM RNA, also designated SEQ ID:3579.

[33099] Another function of VGAM868 is therefore inhibition of DKFZP434A043 (Accession NM\_015396). Accordingly, utilities of VGAM868 include diagnosis, prevention and



treatment of diseases and clinical conditions associated with DKFZP434A043. LOC221074 (Accession XM\_167663) is another VGAM868 host target gene. LOC221074 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221074, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221074 BINDING SITE, designated SEQ ID:44748, to the nucleotide sequence of VGAM868 RNA, herein designated VGAM RNA, also designated SEQ ID:3579.

[33100] Another function of VGAM868 is therefore inhibition of LOC221074 (Accession XM\_167663). Accordingly, utilities of VGAM868 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221074. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 869 (VGAM869) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33101] VGAM869 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM869 was detected is described hereinabove with reference to Figs. 1–8.

[33102] VGAM869 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM869 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33103] VGAM869 gene encodes a VGAM869 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM869 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM869 precursor RNA is designated SEQ ID:855, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:855 is located at position 174898 relative to the genome of Fowlpox Virus.

[33104] VGAM869 precursor RNA folds onto itself, forming VGAM869 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33105] An enzyme complex designated DICER COMPLEX, `dices` the VGAM869 folded precursor RNA into VGAM869 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 50%) nucleotide sequence of VGAM869 RNA is designated SEQ ID:3580, and is provided hereinbelow with reference to the sequence listing part.

[33106] VGAM869 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM869 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM869 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33107] VGAM869 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM869 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM869 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM869 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM869 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33108] The complementary binding of VGAM869 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM869 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM869 host target RNA into VGAM869 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33109] It is appreciated that VGAM869 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM869 host target genes. The mRNA of each one of this plurality of VGAM869 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM869 RNA, herein designated VGAM RNA, and which when bound by VGAM869 RNA causes inhibition of translation of respective one or more VGAM869 host target proteins.

[33110] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM869 gene, herein designated VGAM GENE, on one or more VGAM869 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33111] It is yet further appreciated that a function of VGAM869 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM869 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM869 correlate with, and may be deduced from, the identity of the host target genes which VGAM869 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33112] Nucleotide sequences of the VGAM869 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM869 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM869 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM869 are further described hereinbelow with reference to Table 1.

[33113] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM869 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM869 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33114] As mentioned hereinabove with reference to Fig. 1, a function of VGAM869 gene, herein designated VGAM is inhibition of expression of VGAM869 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM869 correlate with, and may be deduced from, the identity of the target genes which VGAM869 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33115] MLL Septin-like Fusion (MSF, Accession XM\_113892) is a VGAM869 host target gene. MSF BINDING SITE is HOST TARGET binding site found in the 3` untranslated region

of mRNA encoded by MSF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSF BINDING SITE, designated SEQ ID:42518, to the nucleotide sequence of VGAM869 RNA, herein designated VGAM RNA, also designated SEQ ID:3580.

[33116] A function of VGAM869 is therefore inhibition of MLL Septin-like Fusion (MSF, Accession XM\_113892), a gene which plays a role in the cell cycle. Accordingly, utilities of VGAM869 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSF. The function of MSF and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM514. Single-minded Homolog 2 (Drosophila) (SIM2, Accession NM\_005069) is another VGAM869 host target gene. SIM2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIM2 BINDING SITE, designated SEQ ID:11515,



to the nucleotide sequence of VGAM869 RNA, herein designated VGAM RNA, also designated SEQ ID:3580.

[33117] Another function of VGAM869 is therefore inhibition of Single-minded Homolog 2 (Drosophila) (SIM2, Accession NM\_005069), a gene which may be a master gene of CNS development. Accordingly, utilities of VGAM869 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIM2. The function of SIM2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM369. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 870 (VGAM870) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33118] VGAM870 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM870 was detected is described hereinabove with reference to Figs. 1–8.

[33119] VGAM870 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM870 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33120] VGAM870 gene encodes a VGAM870 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM870 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM870 precursor RNA is designated SEQ ID:856, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:856 is located at position 175174 relative to the genome of Fowlpox Virus.

[33121] VGAM870 precursor RNA folds onto itself, forming VGAM870 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33122] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM870 folded precursor RNA into VGAM870 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM870 RNA is designated SEQ ID:3581, and is provided hereinbelow with reference to the sequence listing part.

[33123] VGAM870 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM870 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM870 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33124] VGAM870 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM870 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM870 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM870 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM870 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33125] The complementary binding of VGAM870 RNA, herein designated VGAM RNA, to host target binding sites on VGAM870 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM870 host target RNA into VGAM870 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33126] It is appreciated that VGAM870 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM870 host target genes. The mRNA of each one of this plurality of VGAM870 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM870 RNA, herein designated VGAM RNA, and which when bound by VGAM870 RNA causes inhibition of translation of respective one or more VGAM870 host target proteins.

[33127] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM870 gene, herein designated VGAM GENE, on one or more VGAM870 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33128] It is yet further appreciated that a function of VGAM870 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM870 correlate with, and may be deduced from, the identity of the host target genes which VGAM870 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33129] Nucleotide sequences of the VGAM870 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM870 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM870 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM870 are further described hereinbelow with reference to Table 1.

- [33130] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM870 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM870 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33131] As mentioned hereinabove with reference to Fig. 1, a function of VGAM870 gene, herein designated VGAM is inhibition of expression of VGAM870 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM870 correlate with, and may be deduced from, the identity of the target genes which VGAM870 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [33132] Contactin Associated Protein-like 2 (CNTNAP2, Accession NM\_014141) is a VGAM870 host target gene. CNTNAP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNTNAP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNTNAP2 BINDING SITE, designated SEQ

ID:15421, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33133] A function of VGAM870 is therefore inhibition of Contactin Associated Protein-like 2 (CNTNAP2, Accession NM\_014141). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNTNAP2. Fibroblast Growth Factor 5 (FGF5, Accession NM\_004464) is another VGAM870 host target gene. FGF5 BINDING SITE1 and FGF5 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGF5, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF5 BINDING SITE1 and FGF5 BINDING SITE2, designated SEQ ID:10777 and SEQ ID:27004 respectively, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33134] Another function of VGAM870 is therefore inhibition of Fibroblast Growth Factor 5 (FGF5, Accession NM\_004464), a gene which induces transformation and may regulate neuronal differentiation. Accordingly, utilities of VGAM870 in-



clude diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF5. The function of FGF5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM276.V-myb Myeloblastosis Viral Oncogene Homolog (avian)-like 1 (MYBL1, Accession XM\_034274) is another VGAM870 host target gene. MYBL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYBL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYBL1 BINDING SITE, designated SEQ ID:32042, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33135] Another function of VGAM870 is therefore inhibition of V-myb Myeloblastosis Viral Oncogene Homolog (avian)-like 1 (MYBL1, Accession XM\_034274), a gene which could have a role in the proliferation and/or differentiation of neurogenic, spermatogenic and b-lymphoid cells. Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associ-

ated with MYBL1. The function of MYBL1 and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM184. Crn, Crooked Neck-like 1 (Drosophila) (CRNKL1, Accession NM\_016652) is another VGAM870 host target gene. CRNKL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRNKL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRNKL1 BINDING SITE, designated SEQ ID:18772, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33136] Another function of VGAM870 is therefore inhibition of Crn, Crooked Neck-like 1 (Drosophila) (CRNKL1, Accession NM\_016652). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRNKL1. FLJ11142 (Accession NM\_018338) is another VGAM870 host target gene. FLJ11142 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11142, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11142 BINDING SITE, designated SEQ ID:20344, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33137] Another function of VGAM870 is therefore inhibition of FLJ11142 (Accession NM\_018338). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11142. FLJ12770 (Accession NM\_032174) is another VGAM870 host target gene. FLJ12770 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12770, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12770 BINDING SITE, designated SEQ ID:25883, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33138] Another function of VGAM870 is therefore inhibition of FLJ12770 (Accession NM\_032174). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ12770. KIAA0275 (Accession NM\_014767) is another VGAM870 host target gene. KIAA0275 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0275, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0275 BINDING SITE, designated SEQ ID:16552, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33139] Another function of VGAM870 is therefore inhibition of KIAA0275 (Accession NM\_014767). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0275. NIR3 (Accession XM\_038799) is another VGAM870 host target gene. NIR3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NIR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NIR3 BINDING SITE, designated SEQ ID:32924, to the nucleotide sequence of

VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33140] Another function of VGAM870 is therefore inhibition of NIR3 (Accession XM\_038799). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NIR3. PRMT6 (Accession NM\_018137) is another VGAM870 host target gene. PRMT6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRMT6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRMT6 BINDING SITE, designated SEQ ID:19933, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33141] Another function of VGAM870 is therefore inhibition of PRMT6 (Accession NM\_018137). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRMT6. Syntaxin 6 (STX6, Accession NM\_005819) is another VGAM870 host target gene. STX6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by STX6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STX6 BINDING SITE, designated SEQ ID:12420, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33142] Another function of VGAM870 is therefore inhibition of Syntaxin 6 (STX6, Accession NM\_005819). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STX6. LOC146059 (Accession XM\_085300) is another VGAM870 host target gene. LOC146059 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146059, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146059 BINDING SITE, designated SEQ ID:38052, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33143] Another function of VGAM870 is therefore inhibition of LOC146059 (Accession XM\_085300). Accordingly, utilities

of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146059. LOC51107 (Accession NM\_016022) is another VGAM870 host target gene. LOC51107 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC51107, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51107 BINDING SITE, designated SEQ ID:18097, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33144] Another function of VGAM870 is therefore inhibition of LOC51107 (Accession NM\_016022). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51107. LOC91408 (Accession XM\_038290) is another VGAM870 host target gene. LOC91408 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC91408, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC91408 BINDING SITE, designated SEQ ID:32789, to the nucleotide sequence of VGAM870 RNA, herein designated VGAM RNA, also designated SEQ ID:3581.

[33145] Another function of VGAM870 is therefore inhibition of LOC91408 (Accession XM\_038290). Accordingly, utilities of VGAM870 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91408. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 871 (VGAM871) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33146] VGAM871 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM871 was detected is described hereinabove with reference to Figs. 1–8.

[33147] VGAM871 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM871 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.



[33148] VGAM871 gene encodes a VGAM871 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM871 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM871 precursor RNA is designated SEQ ID:857, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:857 is located at position 172281 relative to the genome of Fowlpox Virus.

[33149] VGAM871 precursor RNA folds onto itself, forming VGAM871 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33150] An enzyme complex designated DICER COMPLEX, `dices` the VGAM871 folded precursor RNA into VGAM871 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM871 RNA is designated SEQ ID:3582, and is provided hereinbelow with reference to the sequence listing part.

[33151] VGAM871 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM871 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM871 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33152] VGAM871 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM871 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM871 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM871 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM871 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33153] The complementary binding of VGAM871 RNA, herein designated VGAM RNA, to host target binding sites on VGAM871 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM871 host target RNA into VGAM871 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33154] It is appreciated that VGAM871 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM871 host target genes. The mRNA of each one of this plurality of VGAM871 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM871 RNA, herein designated VGAM RNA, and which when bound by VGAM871 RNA causes inhibition of translation of respective one or more VGAM871 host target proteins.

[33155] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM871 gene, herein designated VGAM GENE, on one or more VGAM871 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[33156] It is yet further appreciated that a function of VGAM871 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM871 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM871 correlate with, and may be deduced from, the identity of the host target genes which VGAM871 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33157] Nucleotide sequences of the VGAM871 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM871 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM871 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM871 are further described hereinbelow with reference to Table 1.

[33158] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM871 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM871 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33159] As mentioned hereinabove with reference to Fig. 1, a function of VGAM871 gene, herein designated VGAM is inhibition of expression of VGAM871 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM871 correlate with, and may be deduced from, the identity of the target genes which VGAM871 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33160] KIAA0677 (Accession NM\_014663) is a VGAM871 host target gene. KIAA0677 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0677, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0677 BINDING SITE, designated SEQ ID:16111, to the nucleotide sequence of VGAM871 RNA, herein designated VGAM RNA, also designated SEQ ID:3582.

[33161] A function of VGAM871 is therefore inhibition of

KIAA0677 (Accession NM\_014663). Accordingly, utilities of VGAM871 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0677. LOC90777 (Accession XM\_034052) is another VGAM871 host target gene. LOC90777 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90777, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90777 BINDING SITE, designated SEQ ID:31994, to the nucleotide sequence of VGAM871 RNA, herein designated VGAM RNA, also designated SEQ ID:3582.

[33162] Another function of VGAM871 is therefore inhibition of LOC90777 (Accession XM\_034052). Accordingly, utilities of VGAM871 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90777. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 872 (VGAM872) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[33163] VGAM872 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM872 was detected is described hereinabove with reference to Figs. 1–8.

[33164] VGAM872 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus. VGAM872 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33165] VGAM872 gene encodes a VGAM872 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM872 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM872 precursor RNA is designated SEQ ID:858, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:858 is located at position 172697 relative to the genome of Fowlpox Virus.

[33166] VGAM872 precursor RNA folds onto itself, forming VGAM872 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional



`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[33167] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM872 folded precursor RNA into VGAM872 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 72%) nucleotide se-  
quence of VGAM872 RNA is designated SEQ ID:3583, and  
is provided hereinbelow with reference to the sequence  
listing part.

[33168] VGAM872 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM872 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM872 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33169] VGAM872 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM872 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM872 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM872 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM872 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[33170] The complementary binding of VGAM872 RNA, herein designated VGAM RNA, to host target binding sites on VGAM872 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM872 host target RNA into VGAM872 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33171] It is appreciated that VGAM872 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM872 host target genes. The mRNA of each one of this plurality of VGAM872 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM872 RNA, herein designated VGAM RNA, and which when bound by VGAM872 RNA causes inhibition of translation of respective one or more VGAM872 host target proteins.

[33172] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM872 gene, herein designated VGAM GENE, on one or

more VGAM872 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33173] It is yet further appreciated that a function of VGAM872 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM872 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM872 correlate with, and may be deduced from, the identity of the host target genes which VGAM872 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [33174] Nucleotide sequences of the VGAM872 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM872 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM872 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM872 are further described hereinbelow with reference to Table 1.
- [33175] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM872 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM872 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33176] As mentioned hereinabove with reference to Fig. 1, a function of VGAM872 gene, herein designated VGAM is inhibition of expression of VGAM872 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM872 correlate with, and may be deduced from, the identity of the target genes which VGAM872 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [33177] Integral Membrane Protein 2B (ITM2B, Accession

NM\_021999) is a VGAM872 host target gene. ITM2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITM2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITM2B BINDING SITE, designated SEQ ID:22537, to the nucleotide sequence of VGAM872 RNA, herein designated VGAM RNA, also designated SEQ ID:3583.

[33178] A function of VGAM872 is therefore inhibition of Integral Membrane Protein 2B (ITM2B, Accession NM\_021999), a gene which is a member of the type II integral membrane protein family. Accordingly, utilities of VGAM872 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITM2B. The function of ITM2B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM458.DKFZP434G1411 (Accession XM\_166383) is another VGAM872 host target gene. DKFZP434G1411 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434G1411, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434G1411 BINDING SITE, designated SEQ ID:44228, to the nucleotide sequence of VGAM872 RNA, herein designated VGAM RNA, also designated SEQ ID:3583.

[33179] Another function of VGAM872 is therefore inhibition of DKFZP434G1411 (Accession XM\_166383). Accordingly, utilities of VGAM872 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434G1411. LOC151103 (Accession XM\_098004) is another VGAM872 host target gene. LOC151103 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151103 BINDING SITE, designated SEQ ID:41298, to the nucleotide sequence of VGAM872 RNA, herein designated VGAM RNA, also designated SEQ ID:3583.

[33180] Another function of VGAM872 is therefore inhibition of LOC151103 (Accession XM\_098004). Accordingly, utilities

of VGAM872 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151103. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 873 (VGAM873) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33181] VGAM873 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM873 was detected is described hereinabove with reference to Figs. 1–8.

[33182] VGAM873 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Fowlpox Virus.

VGAM873 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33183] VGAM873 gene encodes a VGAM873 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM873 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–



quence of VGAM873 precursor RNA is designated SEQ ID:859, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:859 is located at position 174514 relative to the genome of Fowlpox Virus.

[33184] VGAM873 precursor RNA folds onto itself, forming VGAM873 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33185] An enzyme complex designated DICER COMPLEX, `dices` the VGAM873 folded precursor RNA into VGAM873 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 85%) nucleotide sequence of VGAM873 RNA is designated SEQ ID:3584, and

is provided hereinbelow with reference to the sequence listing part.

[33186] VGAM873 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM873 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM873 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33187] VGAM873 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM873 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM873 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM873 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM873 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33188] The complementary binding of VGAM873 RNA, herein designated VGAM RNA, to host target binding sites on VGAM873 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM873 host target RNA into VGAM873 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33189] It is appreciated that VGAM873 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM873 host target genes. The mRNA of each one of this plurality of VGAM873 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM873 RNA, herein designated VGAM RNA, and which when bound by VGAM873 RNA causes inhibition of translation of respective one or more VGAM873 host target proteins.

[33190] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM873 gene, herein designated VGAM GENE, on one or more VGAM873 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33191] It is yet further appreciated that a function of VGAM873 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of viral infection by Fowlpox Virus. Specific functions, and accordingly utilities, of VGAM873 correlate with, and may be deduced from, the identity of the host target genes which VGAM873 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33192] Nucleotide sequences of the VGAM873 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM873 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM873 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM873 are further described hereinbelow with reference to Table 1.

[33193] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM873 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM873 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33194] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM873 gene, herein designated VGAM is inhibition of expression of VGAM873 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM873 correlate with, and may be deduced from, the identity of the target genes which VGAM873 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33195] Amyloid Beta Precursor Protein (cytoplasmic tail) Binding Protein 2 (APPBP2, Accession NM\_006380) is a VGAM873 host target gene. APPBP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by APPBP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APPBP2 BINDING SITE, designated SEQ ID:13081, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33196] A function of VGAM873 is therefore inhibition of Amyloid Beta Precursor Protein (cytoplasmic tail) Binding Protein 2 (APPBP2, Accession NM\_006380), a gene which interacts with the basolateral sorting signal of amyloid precursor protein. Accordingly, utilities of VGAM873 include diag-

nosis, prevention and treatment of diseases and clinical conditions associated with APPBP2. The function of APPBP2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM525. Cannabinoid Receptor 1 (brain) (CNR1, Accession NM\_016083) is another VGAM873 host target gene. CNR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CNR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNR1 BINDING SITE, designated SEQ ID:18166, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33197] Another function of VGAM873 is therefore inhibition of Cannabinoid Receptor 1 (brain) (CNR1, Accession NM\_016083), a gene which is involved in the cannabinoid-induced CNS effects. Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNR1. The function of CNR1 and its association with various diseases and clinical conditions, has been established by previous

studies, as described hereinabove with reference to VGAM533. Chromosome X Open Reading Frame 6 (CXorf6, Accession NM\_005491) is another VGAM873 host target gene. CXorf6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CXorf6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CXorf6 BINDING SITE, designated SEQ ID:11990, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33198] Another function of VGAM873 is therefore inhibition of Chromosome X Open Reading Frame 6 (CXorf6, Accession NM\_005491). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CXorf6. Isovaleryl Coenzyme A Dehydrogenase (IVD, Accession NM\_002225) is another VGAM873 host target gene. IVD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IVD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-



tarity of the nucleotide sequences of IVD BINDING SITE, designated SEQ ID:8002, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33199] Another function of VGAM873 is therefore inhibition of Isovaleryl Coenzyme A Dehydrogenase (IVD, Accession NM\_002225). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IVD. Membrane-spanning 4-domains, Subfamily A, Member 3 (hematopoietic cell-specific) (MS4A3, Accession NM\_006138) is another VGAM873 host target gene. MS4A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MS4A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MS4A3 BINDING SITE, designated SEQ ID:12778, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33200] Another function of VGAM873 is therefore inhibition of Membrane-spanning 4-domains, Subfamily A, Member 3 (hematopoietic cell-specific) (MS4A3, Accession

NM\_006138). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MS4A3. Myeloma Overexpressed Gene (in a subset of t(11;14) Positive Multiple Myelomas) (MYEOV, Accession NM\_138768) is another VGAM873 host target gene. MYEOV BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MYEOV, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYEOV BINDING SITE, designated SEQ ID:29000, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33201] Another function of VGAM873 is therefore inhibition of Myeloma Overexpressed Gene (in a subset of t(11;14) Positive Multiple Myelomas) (MYEOV, Accession NM\_138768), a gene which is encoded by MYELOMA OVEREXPRESSED GENE. Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYEOV. The function of MYEOV and its association with various diseases and clinical conditions, has been established by previous

studies, as described hereinabove with reference to VGAM471. Protein Phosphatase 1, Catalytic Subunit, Beta Isoform (PPP1CB, Accession NM\_002709) is another VGAM873 host target gene. PPP1CB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1CB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1CB BINDING SITE, designated SEQ ID:8554, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33202] Another function of VGAM873 is therefore inhibition of Protein Phosphatase 1, Catalytic Subunit, Beta Isoform (PPP1CB, Accession NM\_002709), a gene which is the catalytic subunit of protein phosphatase 1. Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1CB. The function of PPP1CB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM46. TEA Domain Family Member 3 (TEAD3, Accession NM\_003214) is another VGAM873 host

target gene. TEAD3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TEAD3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TEAD3 BINDING SITE, designated SEQ ID:9212, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33203] Another function of VGAM873 is therefore inhibition of TEA Domain Family Member 3 (TEAD3, Accession NM\_003214), a gene which binds to multiple functional elements of the human chorionic somatomammotropin- $\beta$  gene enhancer. Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TEAD3. The function of TEAD3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM299. Ubiquitin Specific Protease 6 (Ure-2 oncogene) (USP6, Accession XM\_165948) is another VGAM873 host target gene. USP6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded

by USP6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USP6 BINDING SITE, designated SEQ ID:43812, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33204] Another function of VGAM873 is therefore inhibition of Ubiquitin Specific Protease 6 (Tre-2 oncogene) (USP6, Accession XM\_165948), a gene which has an atp-independent isopeptidase activity, cleaving at the carboxyl terminus of the ubiquitin moiety. Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USP6. The function of USP6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM296. Vang-like 2 (van gogh, Drosophila) (VANGL2, Accession XM\_049695) is another VGAM873 host target gene. VANGL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VANGL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of VANGL2 BINDING SITE, designated SEQ ID:35479, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33205] Another function of VGAM873 is therefore inhibition of Vang-like 2 (van gogh, Drosophila) (VANGL2, Accession XM\_049695), a gene which may take part in defining the lateral boundary of floorplate differentiation. Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with VANGL2. The function of VANGL2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM111. A Kinase (PRKA) Anchor Protein 11 (AKAP11, Accession NM\_016248) is another VGAM873 host target gene. AKAP11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AKAP11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP11 BINDING SITE, designated SEQ ID:18374, to the nucleotide se-

quence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33206] Another function of VGAM873 is therefore inhibition of A Kinase (PRKA) Anchor Protein 11 (AKAP11, Accession NM\_016248). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP11. DJ667H12.2 (Accession NM\_019605) is another VGAM873 host target gene. DJ667H12.2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DJ667H12.2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DJ667H12.2 BINDING SITE, designated SEQ ID:21216, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33207] Another function of VGAM873 is therefore inhibition of DJ667H12.2 (Accession NM\_019605). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DJ667H12.2. FLJ00001 (Accession XM\_088525) is another VGAM873 host target gene. FLJ00001 BINDING SITE is

HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ00001, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ00001 BINDING SITE, designated SEQ ID:39778, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33208] Another function of VGAM873 is therefore inhibition of FLJ00001 (Accession XM\_088525). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ00001. FLJ14007 (Accession NM\_024699) is another VGAM873 host target gene. FLJ14007 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14007, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14007 BINDING SITE, designated SEQ ID:24009, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33209] Another function of VGAM873 is therefore inhibition of



FLJ14007 (Accession NM\_024699). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14007. FLJ23017 (Accession NM\_022840) is another VGAM873 host target gene. FLJ23017 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23017 BINDING SITE, designated SEQ ID:23132, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33210] Another function of VGAM873 is therefore inhibition of FLJ23017 (Accession NM\_022840). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23017. KIAA0229 (Accession XM\_166478) is another VGAM873 host target gene. KIAA0229 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0229, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0229 BINDING SITE, designated SEQ ID:44404, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33211] Another function of VGAM873 is therefore inhibition of KIAA0229 (Accession XM\_166478). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0229. KIAA0285 (Accession NM\_014807) is another VGAM873 host target gene. KIAA0285 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0285, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0285 BINDING SITE, designated SEQ ID:16754, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33212] Another function of VGAM873 is therefore inhibition of KIAA0285 (Accession NM\_014807). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0285. KIAA0513 (Accession NM\_014732) is another

VGAM873 host target gene. KIAA0513 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0513, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0513 BINDING SITE, designated SEQ ID:16362, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33213] Another function of VGAM873 is therefore inhibition of KIAA0513 (Accession NM\_014732). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0513. KIAA1041 (Accession NM\_014947) is another VGAM873 host target gene. KIAA1041 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1041, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1041 BINDING SITE, designated SEQ ID:17263, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33214] Another function of VGAM873 is therefore inhibition of KIAA1041 (Accession NM\_014947). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1041. KIAA1171 (Accession XM\_113868) is another VGAM873 host target gene. KIAA1171 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1171, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1171 BINDING SITE, designated SEQ ID:42481, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33215] Another function of VGAM873 is therefore inhibition of KIAA1171 (Accession XM\_113868). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1171. KIAA1348 (Accession XM\_043826) is another VGAM873 host target gene. KIAA1348 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1348, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1348 BINDING SITE, designated SEQ ID:34027, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33216] Another function of VGAM873 is therefore inhibition of KIAA1348 (Accession XM\_043826). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1348. PLU-1 (Accession NM\_006618) is another VGAM873 host target gene. PLU-1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PLU-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLU-1 BINDING SITE, designated SEQ ID:13403, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33217] Another function of VGAM873 is therefore inhibition of PLU-1 (Accession NM\_006618). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLU-1.

SET Binding Protein 1 (SETBP1, Accession NM\_015559) is another VGAM873 host target gene. SETBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SETBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SETBP1 BINDING SITE, designated SEQ ID:17828, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33218] Another function of VGAM873 is therefore inhibition of SET Binding Protein 1 (SETBP1, Accession NM\_015559). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SETBP1. Transcription Factor 6-like 1 (mitochondrial transcription factor 1-like) (TCF6L1, Accession NM\_003201) is another VGAM873 host target gene. TCF6L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TCF6L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCF6L1 BINDING SITE, designated SEQ

ID:9188, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33219] Another function of VGAM873 is therefore inhibition of Transcription Factor 6-like 1 (mitochondrial transcription factor 1-like) (TCF6L1, Accession NM\_003201). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCF6L1. Ubiquitin-conjugating Enzyme E2D 3 (UBC4/5 homolog, yeast) (UBE2D3, Accession NM\_003340) is another VGAM873 host target gene. UBE2D3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2D3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2D3 BINDING SITE, designated SEQ ID:9346, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33220] Another function of VGAM873 is therefore inhibition of Ubiquitin-conjugating Enzyme E2D 3 (UBC4/5 homolog, yeast) (UBE2D3, Accession NM\_003340). Accordingly, util-

ities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE2D3. LOC153778 (Accession XM\_087762) is another VGAM873 host target gene. LOC153778 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC153778, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153778 BINDING SITE, designated SEQ ID:39408, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33221] Another function of VGAM873 is therefore inhibition of LOC153778 (Accession XM\_087762). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153778. LOC196955 (Accession XM\_085210) is another VGAM873 host target gene. LOC196955 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC196955, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences



of LOC196955 BINDING SITE, designated SEQ ID:37934, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33222] Another function of VGAM873 is therefore inhibition of LOC196955 (Accession XM\_085210). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196955. LOC199858 (Accession XM\_114040) is another VGAM873 host target gene. LOC199858 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199858, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199858 BINDING SITE, designated SEQ ID:42637, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33223] Another function of VGAM873 is therefore inhibition of LOC199858 (Accession XM\_114040). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199858. LOC199870 (Accession XM\_114043) is another VGAM873 host target gene. LOC199870 BINDING

SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199870, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199870 BINDING SITE, designated SEQ ID:42647, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33224] Another function of VGAM873 is therefore inhibition of LOC199870 (Accession XM\_114043). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199870. LOC200488 (Accession XM\_117240) is another VGAM873 host target gene. LOC200488 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200488, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200488 BINDING SITE, designated SEQ ID:43315, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33225] Another function of VGAM873 is therefore inhibition of

LOC200488 (Accession XM\_117240). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200488. LOC200942 (Accession XM\_114323) is another VGAM873 host target gene. LOC200942 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200942, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200942 BINDING SITE, designated SEQ ID:42872, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33226] Another function of VGAM873 is therefore inhibition of LOC200942 (Accession XM\_114323). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200942. LOC202181 (Accession XM\_114456) is another VGAM873 host target gene. LOC202181 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202181, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC202181 BINDING SITE, designated SEQ ID:42968, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33227] Another function of VGAM873 is therefore inhibition of LOC202181 (Accession XM\_114456). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202181. LOC93259 (Accession XM\_050105) is another VGAM873 host target gene. LOC93259 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC93259, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93259 BINDING SITE, designated SEQ ID:35563, to the nucleotide sequence of VGAM873 RNA, herein designated VGAM RNA, also designated SEQ ID:3584.

[33228] Another function of VGAM873 is therefore inhibition of LOC93259 (Accession XM\_050105). Accordingly, utilities of VGAM873 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93259. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 874 (VGAM874) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33229] VGAM874 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM874 was detected is described hereinabove with reference to Figs. 1–8.

[33230] VGAM874 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Swinepox Virus. VGAM874 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33231] VGAM874 gene encodes a VGAM874 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM874 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM874 precursor RNA is designated SEQ ID:860, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:860 is

located at position 91946 relative to the genome of Swinepox Virus.

[33232] VGAM874 precursor RNA folds onto itself, forming VGAM874 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33233] An enzyme complex designated DICER COMPLEX, `dices` the VGAM874 folded precursor RNA into VGAM874 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM874 RNA is designated SEQ ID:3585, and is provided hereinbelow with reference to the sequence listing part.

[33234] VGAM874 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM874 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM874 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33235] VGAM874 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM874 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM874 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM874 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM874 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33236] The complementary binding of VGAM874 RNA, herein designated VGAM RNA, to host target binding sites on VGAM874 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM874 host target RNA into VGAM874 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33237] It is appreciated that VGAM874 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM874 host target genes. The mRNA of each one of this plurality of VGAM874 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM874 RNA, herein designated VGAM RNA, and which when bound by VGAM874 RNA causes inhibition of translation of respective one or more VGAM874



host target proteins.

[33238] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM874 gene, herein designated VGAM GENE, on one or more VGAM874 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33239] It is yet further appreciated that a function of VGAM874 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of viral infection by Swinepox Virus. Specific

functions, and accordingly utilities, of VGAM874 correlate with, and may be deduced from, the identity of the host target genes which VGAM874 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33240] Nucleotide sequences of the VGAM874 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM874 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM874 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM874 are further described hereinbelow with reference to Table 1.

[33241] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM874 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM874 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33242] As mentioned hereinabove with reference to Fig. 1, a function of VGAM874 gene, herein designated VGAM is inhibition of expression of VGAM874 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM874 correlate with, and may be deduced from, the identity of the target genes which VGAM874 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33243] Gamma-aminobutyric Acid (GABA) A Receptor, Alpha 5 (GABRA5, Accession XM\_012441) is a VGAM874 host target gene. GABRA5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GABRA5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GABRA5 BINDING SITE, designated SEQ ID:30213, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33244] A function of VGAM874 is therefore inhibition of Gamma-aminobutyric Acid (GABA) A Receptor, Alpha 5 (GABRA5, Accession XM\_012441), a gene which mediates neuronal inhibition by binding to the gaba/benzodiazepine receptor and opening an integral chloride channel. Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GABRA5. The function of GABRA5 has been estab-

lished by previous studies. Papadimitriou et al. (1998) found an association between a 282-bp CA repeat in the gene encoding GABRA5 and bipolar affective disorder in 48 unrelated southern Greek patients but not in 50 healthy individuals drawn from the same population. No association was seen in another sample of 40 unipolar patients in the same specimen. Even though the authors applied the Bonferroni correction for the total numbers of genes tested, they cautioned that the level of significance in association studies is still a matter of debate. They believed that the 282-bp allele is unlikely to have functional significance but does not represent stratification in their sample. Rather, they considered that the allele may be in linkage disequilibrium with a functional mutation elsewhere in the GABRA5 gene or another gene in close proximity. Ritchie et al. (1998) reported a partial duplication of GABRA5 within the imprinted 15q11-q13 region. The duplicated locus mapped to the pericentromeric region of 15q, proximal to the large deletions associated Angelman and Prader-Willi syndromes. They also observed variation in the number of copies of this locus in different individuals, indicating that the duplication is part of the variable repeat. Investigation of the duplication in individuals with

a normal karyotype revealed between 1 and 4 copies of the repeat on each chromosome 15, whereas from 8 to 20 copies were found in individuals possessing a cytogenetically detectable elongation of the 15q region. The variable region is roughly 1 Mb long and contains 2 other nonprocessed duplications, the immunoglobulin heavy chain (IgH) D segment gene (IGHD; 147170) on 14q and the neurofibromatosis type 1 gene (NF1; 162200) on chromosome 17. One unit of the pericentromeric repeat is thus composed of duplications of genes from different chromosomal regions. Ritchie et al. (1998) also found replication asynchrony across the GABRA5 duplication, suggesting for the first time that the imprinted part of chromosome 15q extends proximal of the region commonly deleted in Angelman and Prader-Willi syndromes.

[33245] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33246] Ritchie, R. J.; Mattei, M.-G.; Lalande, M. : A large polymorphic repeat in the pericentromeric region of human chromosome 15q contains three partial gene duplications. Hum. Molec. Genet. 7: 1253-1260, 1998. ; and

[33247] Papadimitriou, G. N.; Dikeos, D. G.; Karadima, G.;

Avramopoulos, D.; Daskalopoulou, E. G.; Vassilopoulos, D.; Stefanis, C. N. : Association between the GABA-A receptor alpha-5 subunit ge.

[33248] Further studies establishing the function and utilities of GABRA5 are found in John Hopkins OMIM database record ID 137142, and in cited publications numbered 628-634 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Hyaluronan Synthase 2 (HAS2, Accession NM\_005328) is another VGAM874 host target gene. HAS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HAS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HAS2 BINDING SITE, designated SEQ ID:11800, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33249] Another function of VGAM874 is therefore inhibition of Hyaluronan Synthase 2 (HAS2, Accession NM\_005328), a gene which plays a role in hyaluronan/hyaluronic acid (ha) synthesis and transport . Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with HAS2. The function of HAS2 has been established by previous studies. Hyaluronan, or hyaluronic acid (HA), is a high molecular weight unbranched polysaccharide of the extracellular matrix. Watanabe and Yamaguchi (1996) described the cloning of a human cDNA from a fibroblast library using degenerate PCR with primers based on regions of conservation between the previously published *Xenopus* DG42 and *Streptococcus* HasA proteins. When expressed in cell culture, the cDNA increased hyaluronan production. The sequence of the predicted 552-amino acid protein differs from HAS1 (OMIM Ref. No. 601463) and so was designated HAS2. The HAS2 amino acid sequence is 55% similar to the *Xenopus* DG42 sequence and 55% identical to mouse Has1. Northern blots showed high levels of HAS2 mRNA in a proliferating human fibroblast cell line but not in growth-arrested cells. Watanabe and Yamaguchi (1996) speculated that if HAS2 is not a true hyaluronan synthase, it is at least a major inducer of HA synthase activity. Spicer et al. (1996) isolated the apparent mouse homolog of human HAS2 from a mouse embryo cDNA library using degenerate PCR. The predicted mouse protein is also 552 amino acids long. The Has2 protein is predicted to contain

multiple transmembrane domains similar to bacterial HasA and mammalian HAS1. Northern blots demonstrated 4.8- and 3.2-kb transcripts expressed highly in the mouse embryo and at lower levels in adult heart, brain, spleen, lung, and skeletal muscle. When expressed in COS cells, the cDNA was shown to induce the formation of large HA coats around the cells. Based on analogy with what is known about HA production in *Streptococcus*, Spicer et al. (1996) suggested that HAS2 may play a key role in HA transport rather than act as a synthase per se.

[33250] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33251] Watanabe, K.; Yamaguchi, Y. : Molecular identification of a putative human hyaluronan synthase. *J. Biol. Chem.* 271: 22945–22948, 1996. ; and

[33252] Spicer, A. P.; Augustine, M. L.; McDonald, J. A. : Molecular cloning and characterization of a putative mouse hyaluronan synthase. *J. Biol. Chem.* 271: 23400–23406, 1996.

[33253] Further studies establishing the function and utilities of HAS2 are found in John Hopkins OMIM database record ID 601636, and in cited publications numbered 6682–2755 listed in the bibliography section hereinbelow, which are



also hereby incorporated by reference. RalA Binding Protein 1 (RALBP1, Accession NM\_006788) is another VGAM874 host target gene. RALBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RALBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RALBP1 BINDING SITE, designated SEQ ID:13656, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33254] Another function of VGAM874 is therefore inhibition of RalA Binding Protein 1 (RALBP1, Accession NM\_006788), a gene which plays a role in signal transduction and catalyzes the transport of glutathione conjugates and xenobiotics. Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RALBP1. The function of RALBP1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM345. WTAP (Accession NM\_004906) is another VGAM874 host target gene. WTAP BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by WTAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WTAP BINDING SITE, designated SEQ ID:11344, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33255] Another function of VGAM874 is therefore inhibition of WTAP (Accession NM\_004906), a gene which plays a role in both transcriptional and posttranscriptional regulation of certain cellular genes. Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WTAP. The function of WTAP has been established by previous studies. The Wilms tumor suppressor gene WT1 (OMIM Ref. No. 607102) appears to play a role in both transcriptional and posttranscriptional regulation of certain cellular genes. Little et al. (2000) used the yeast 2-hybrid system to identify a novel human WT1-associating protein, which they called WTAP, containing 388 amino acids. They also identified the mouse homolog and found that the 2 proteins share 96% sequence identity. Both in vitro and in vivo assays demonstrated a specific interaction between

WTAP and WT1, which occurred endogenously in cells.

The authors found that WTAP is a ubiquitously expressed nuclear protein which, like WT1, localized throughout the nucleoplasm as well as in speckles and partially colocalized with splicing factors. Using a panel of human-rodent hybrid cell lines, Nagase et al. (1995) mapped the WTAP gene, which they designated KIAA0105, to chromosome 6. By fluorescence in situ hybridization, Little et al. (2000) assigned the human WTAP gene to chromosome 6q25-q27 and the mouse homolog to a region of syntenic homology on chromosome 17

[33256] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33257] Little, N. A.; Hastie, N. D.; Davies, R. C. : Identification of WTAP, a novel Wilms' tumour 1-associating protein. Hum. Molec. Genet. 9: 2231-2239, 2000. ; and

[33258] Nagase, T.; Miyajima, N.; Tanaka, A.; Sazuka, T.; Seki, N.; Sato, S.; Tabata, S.; Ishikawa, K.; Kawarabayasi, Y.; Kotani, H.; Nomura, N. : Prediction of the coding sequences of unidentified.

[33259] Further studies establishing the function and utilities of WTAP are found in John Hopkins OMIM database record ID

605442, and in cited publications numbered 5025 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cysteine and Tyrosine-rich 1 (CYR1, Accession NM\_052954) is another VGAM874 host target gene. CYR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYR1 BINDING SITE, designated SEQ ID:27515, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33260] Another function of VGAM874 is therefore inhibition of Cysteine and Tyrosine-rich 1 (CYR1, Accession NM\_052954). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYR1. FLJ21945 (Accession NM\_025203) is another VGAM874 host target gene. FLJ21945 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ21945, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21945 BINDING SITE, designated SEQ ID:24867, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33261] Another function of VGAM874 is therefore inhibition of FLJ21945 (Accession NM\_025203). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21945. HTEX4 (Accession XM\_166378) is another VGAM874 host target gene. HTEX4 BINDING SITE1 through HTEX4 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HTEX4, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HTEX4 BINDING SITE1 through HTEX4 BINDING SITE3, designated SEQ ID:44214, SEQ ID:46650 and SEQ ID:46719 respectively, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33262] Another function of VGAM874 is therefore inhibition of HTEX4 (Accession XM\_166378). Accordingly, utilities of

VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HTEX4. LOC147353 (Accession XM\_097227) is another VGAM874 host target gene. LOC147353 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC147353, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147353 BINDING SITE, designated SEQ ID:40837, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33263] Another function of VGAM874 is therefore inhibition of LOC147353 (Accession XM\_097227). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147353. LOC148530 (Accession XM\_097480) is another VGAM874 host target gene. LOC148530 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148530, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC148530 BINDING SITE, designated SEQ ID:40887, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33264] Another function of VGAM874 is therefore inhibition of LOC148530 (Accession XM\_097480). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148530. LOC149827 (Accession XM\_097762) is another VGAM874 host target gene. LOC149827 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149827, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149827 BINDING SITE, designated SEQ ID:41111, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33265] Another function of VGAM874 is therefore inhibition of LOC149827 (Accession XM\_097762). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149827. LOC158490 (Accession XM\_088585) is another VGAM874 host target gene. LOC158490 BINDING

SITE is HOST TARGET binding site found in the 3` un-translated region of mRNA encoded by LOC158490, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158490 BINDING SITE, designated SEQ ID:39847, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33266] Another function of VGAM874 is therefore inhibition of LOC158490 (Accession XM\_088585). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158490. LOC196484 (Accession XM\_031807) is another VGAM874 host target gene. LOC196484 BINDING SITE is HOST TARGET binding site found in the 5` un-translated region of mRNA encoded by LOC196484, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196484 BINDING SITE, designated SEQ ID:31484, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33267] Another function of VGAM874 is therefore inhibition of



LOC196484 (Accession XM\_031807). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196484. LOC220073 (Accession XM\_167847) is another VGAM874 host target gene. LOC220073 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC220073, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220073 BINDING SITE, designated SEQ ID:44872, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33268] Another function of VGAM874 is therefore inhibition of LOC220073 (Accession XM\_167847). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220073. LOC222160 (Accession XM\_168431) is another VGAM874 host target gene. LOC222160 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC222160, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC222160 BINDING SITE, designated SEQ ID:45164, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33269] Another function of VGAM874 is therefore inhibition of LOC222160 (Accession XM\_168431). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222160. LOC91069 (Accession XM\_035824) is another VGAM874 host target gene. LOC91069 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91069, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91069 BINDING SITE, designated SEQ ID:32344, to the nucleotide sequence of VGAM874 RNA, herein designated VGAM RNA, also designated SEQ ID:3585.

[33270] Another function of VGAM874 is therefore inhibition of LOC91069 (Accession XM\_035824). Accordingly, utilities of VGAM874 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91069. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 875 (VGAM875) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33271] VGAM875 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM875 was detected is described hereinabove with reference to Figs. 1–8.

[33272] VGAM875 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 5. VGAM875 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33273] VGAM875 gene encodes a VGAM875 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM875 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM875 precursor RNA is designated SEQ ID:861, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:861 is

located at position 28481 relative to the genome of Human Herpesvirus 5.

[33274] VGAM875 precursor RNA folds onto itself, forming VGAM875 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33275] An enzyme complex designated DICER COMPLEX, `dices` the VGAM875 folded precursor RNA into VGAM875 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 67%) nucleotide sequence of VGAM875 RNA is designated SEQ ID:3586, and is provided hereinbelow with reference to the sequence listing part.

[33276] VGAM875 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM875 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM875 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33277] VGAM875 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM875 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM875 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM875 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM875 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[33278] The complementary binding of VGAM875 RNA, herein designated VGAM RNA, to host target binding sites on VGAM875 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM875 host target RNA into VGAM875 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33279] It is appreciated that VGAM875 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM875 host target genes. The mRNA of each one of this plurality of VGAM875 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM875 RNA, herein designated VGAM RNA, and which when bound by VGAM875 RNA causes inhibition of translation of respective one or more VGAM875

host target proteins.

[33280] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM875 gene, herein designated VGAM GENE, on one or more VGAM875 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33281] It is yet further appreciated that a function of VGAM875 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM875 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 5. Spe-

cific functions, and accordingly utilities, of VGAM875 correlate with, and may be deduced from, the identity of the host target genes which VGAM875 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33282] Nucleotide sequences of the VGAM875 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM875 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM875 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM875 are further described hereinbelow with reference to Table 1.

[33283] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM875 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM875 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33284] As mentioned hereinabove with reference to Fig. 1, a function of VGAM875 gene, herein designated VGAM is inhibition of expression of VGAM875 target genes. It is appreciated that specific functions, and accordingly utili-



ties, of VGAM875 correlate with, and may be deduced from, the identity of the target genes which VGAM875 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33285] MGC10818 (Accession NM\_030568) is a VGAM875 host target gene. MGC10818 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC10818, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC10818 BINDING SITE, designated SEQ ID:24942, to the nucleotide sequence of VGAM875 RNA, herein designated VGAM RNA, also designated SEQ ID:3586.

[33286] A function of VGAM875 is therefore inhibition of MGC10818 (Accession NM\_030568). Accordingly, utilities of VGAM875 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC10818. SV2B (Accession NM\_014848) is another VGAM875 host target gene. SV2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SV2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE

II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SV2B BINDING SITE, designated SEQ ID:16881, to the nucleotide sequence of VGAM875 RNA, herein designated VGAM RNA, also designated SEQ ID:3586.

[33287] Another function of VGAM875 is therefore inhibition of SV2B (Accession NM\_014848). Accordingly, utilities of VGAM875 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SV2B. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 876 (VGAM876) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33288] VGAM876 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM876 was detected is described hereinabove with reference to Figs. 1–8.

[33289] VGAM876 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 5. VGAM876 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[33290] VGAM876 gene encodes a VGAM876 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM876 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM876 precursor RNA is designated SEQ ID:862, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:862 is located at position 29679 relative to the genome of Human Herpesvirus 5.

[33291] VGAM876 precursor RNA folds onto itself, forming VGAM876 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33292] An enzyme complex designated DICER COMPLEX, `dices` the VGAM876 folded precursor RNA into VGAM876 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM876 RNA is designated SEQ ID:3587, and is provided hereinbelow with reference to the sequence listing part.

[33293] VGAM876 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM876 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM876 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33294] VGAM876 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM876 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM876 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM876 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM876 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33295] The complementary binding of VGAM876 RNA, herein designated VGAM RNA, to host target binding sites on VGAM876 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM876 host target RNA into VGAM876 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33296] It is appreciated that VGAM876 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM876 host target genes. The mRNA of each one of this plurality of VGAM876 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM876 RNA, herein designated VGAM RNA, and which when bound by VGAM876 RNA causes inhibition of translation of respective one or more VGAM876 host target proteins.

[33297] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM876 gene, herein designated VGAM GENE, on one or more VGAM876 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33298] It is yet further appreciated that a function of VGAM876 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM876 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 5. Specific functions, and accordingly utilities, of VGAM876 correlate with, and may be deduced from, the identity of the host target genes which VGAM876 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33299] Nucleotide sequences of the VGAM876 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM876 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM876 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM876 are further described hereinbelow with reference to Table 1.

[33300] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM876 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM876 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33301] As mentioned hereinabove with reference to Fig. 1, a function of VGAM876 gene, herein designated VGAM is inhibition of expression of VGAM876 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM876 correlate with, and may be deduced from, the identity of the target genes which VGAM876 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33302] EH-domain Containing 2 (EHD2, Accession NM\_014601) is a VGAM876 host target gene. EHD2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EHD2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EHD2 BINDING SITE, designated SEQ ID:15960, to the nucleotide sequence of VGAM876 RNA, herein designated VGAM RNA, also designated SEQ ID:3587.



[33303] A function of VGAM876 is therefore inhibition of EH-domain Containing 2 (EHD2, Accession NM\_014601). Accordingly, utilities of VGAM876 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EHD2. LOC51289 (Accession NM\_016568) is another VGAM876 host target gene. LOC51289 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51289, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51289 BINDING SITE, designated SEQ ID:18639, to the nucleotide sequence of VGAM876 RNA, herein designated VGAM RNA, also designated SEQ ID:3587.

[33304] Another function of VGAM876 is therefore inhibition of LOC51289 (Accession NM\_016568). Accordingly, utilities of VGAM876 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51289. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 877 (VGAM877) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[33305] VGAM877 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM877 was detected is described hereinabove with reference to Figs. 1–8.

[33306] VGAM877 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 5. VGAM877 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33307] VGAM877 gene encodes a VGAM877 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM877 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM877 precursor RNA is designated SEQ ID:863, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:863 is located at position 27633 relative to the genome of Human Herpesvirus 5.

[33308] VGAM877 precursor RNA folds onto itself, forming VGAM877 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[33309] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM877 folded precursor RNA into VGAM877 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 79%) nucleotide se-  
quence of VGAM877 RNA is designated SEQ ID:3588, and  
is provided hereinbelow with reference to the sequence  
listing part.

[33310] VGAM877 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM877 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM877 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33311] VGAM877 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM877 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM877 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM877 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM877 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33312] The complementary binding of VGAM877 RNA, herein designated VGAM RNA, to host target binding sites on VGAM877 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM877 host target RNA into VGAM877 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33313] It is appreciated that VGAM877 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM877 host target genes. The mRNA of each one of this plurality of VGAM877 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM877 RNA, herein designated VGAM RNA, and which when bound by VGAM877 RNA causes inhibition of translation of respective one or more VGAM877 host target proteins.

[33314] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM877 gene, herein designated VGAM GENE, on one or more VGAM877 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33315] It is yet further appreciated that a function of VGAM877 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 5. Specific functions, and accordingly utilities, of VGAM877 correlate with, and may be deduced from, the identity of the host target genes which VGAM877 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

- [33316] Nucleotide sequences of the VGAM877 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM877 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM877 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM877 are further described hereinbelow with reference to Table 1.
- [33317] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM877 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM877 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33318] As mentioned hereinabove with reference to Fig. 1, a function of VGAM877 gene, herein designated VGAM is inhibition of expression of VGAM877 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM877 correlate with, and may be deduced from, the identity of the target genes which VGAM877 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33319] Catenin (cadherin-associated protein), Alpha 2 (CTNNA2, Accession NM\_004389) is a VGAM877 host target gene. CTNNA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CTNNA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CTNNA2 BINDING SITE, designated SEQ ID:10618, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33320] A function of VGAM877 is therefore inhibition of Catenin (cadherin-associated protein), Alpha 2 (CTNNA2, Accession NM\_004389), a gene which is involved in the cytoplasmic anchorage of cell-cell and cell-substrate adhesion molecules. Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CTNNA2. The function of CTNNA2 has been established by previous studies. Cell-cell and cell-matrix adhesions involve transmembrane glycoproteins such as cell adhesion molecules and integrins, which are thought to function via interactions of their cytoplasmic domains with proteins associated with



the cytoskeleton. Vinculin (OMIM Ref. No. 193065) and talin (OMIM Ref. No. 186745) are examples. The activity of cadherins (e.g., 114020), which mediate homophilic cell-cell  $\text{Ca}^{2+}$ -dependent association, depends on their anchorage to cytoskeleton via proteins termed catenins (Herrenknecht et al., 1991). Animal model experiments lend further support to the function of CTNNA2. Mice homozygous for the 'cerebellar-deficient folia' (cdf) mutation are ataxic and have cerebellar hypoplasia and abnormal lobulation of the cerebellum (Cook et al., 1997). In the cerebella of cdf/cdf homozygous mice, approximately 40% of Purkinje cells are located ectopically in the white matter and inner granule-cell layer. Many hippocampal pyramidal cells are scattered in the plexiform layers, and those that are correctly positioned are less densely packed than are cells in wildtype mice. Park et al. (2002) showed that fear conditioning and prepulse inhibition of the startle response are also disrupted in cdf/cdf mice. They identified a deletion on mouse chromosome 6 that removed approximately 150 kb of the cdf region. The deletion included part of *Catna2*, encoding alpha-N-catenin, a protein that links the classic cadherins to the neuronal cytoskeleton. Expression of a *Catna2* transgene in cdf/cdf

mice restored normal cerebellar and hippocampal morphology, prepulse inhibition, and fear conditioning. The findings suggested that catenin–cadherin cell–adhesion complexes are important in cerebellar and hippocampal lamination and in the control of startle modulation.

[33321] It is appreciated that the abovementioned animal model for CTNNA2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[33322] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33323] Claverie, J.–M.; Hardelin, J.–P.; Legouis, R.; Levilliers, J.; Bougueleret, L.; Mattei, M.–G.; Petit, C. : Characterization and chromosomal assignment of a human cDNA encoding a protein related to the murine 102–kDa cadherin–associated protein (alpha–catenin). *Genomics* 15: 13–20, 1993. ; and

[33324] Park, C.; Falls, W.; Finger, J. H.; Longo–Guess, C. M.; Ackerman, S. L. : Deletion in *Catna2*, encoding alpha–N–catenin, causes cerebellar and hippocampal lamination defects and impaired.

[33325] Further studies establishing the function and utilities of

CTNNA2 are found in John Hopkins OMIM database record ID 114025, and in cited publications numbered 11654–11655, 982 and 11656–11657 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Kallmann Syndrome 1 Sequence (KAL1, Accession NM\_000216) is another VGAM877 host target gene. KAL1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KAL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KAL1 BINDING SITE, designated SEQ ID:5716, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33326] Another function of VGAM877 is therefore inhibition of Kallmann Syndrome 1 Sequence (KAL1, Accession NM\_000216). Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KAL1. Nijmegen Breakage Syndrome 1 (nibrin) (NBS1, Accession XM\_045343) is another VGAM877 host target gene. NBS1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated

region of mRNA encoded by NBS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NBS1 BINDING SITE, designated SEQ ID:34436, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33327] Another function of VGAM877 is therefore inhibition of Nijmegen Breakage Syndrome 1 (nibrin) (NBS1, Accession XM\_045343), a gene which may be involved in repair of DNA double-strand breaks. Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NBS1. The function of NBS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM450. Oligophrenin 1 (OPHN1, Accession NM\_002547) is another VGAM877 host target gene. OPHN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by OPHN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

OPHN1 BINDING SITE, designated SEQ ID:8403, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33328] Another function of VGAM877 is therefore inhibition of Oligophrenin 1 (OPHN1, Accession NM\_002547). Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with OPHN1. A Kinase (PRKA) Anchor Protein 7 (AKAP7, Accession NM\_004842) is another VGAM877 host target gene. AKAP7 BINDING SITE1 through AKAP7 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by AKAP7, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AKAP7 BINDING SITE1 through AKAP7 BINDING SITE3, designated SEQ ID:11253, SEQ ID:18516 and SEQ ID:28906 respectively, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33329] Another function of VGAM877 is therefore inhibition of A Kinase (PRKA) Anchor Protein 7 (AKAP7, Accession NM\_004842). Accordingly, utilities of VGAM877 include

diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP7. Histidyl-tRNA Synthetase-like (HARSL, Accession NM\_012208) is another VGAM877 host target gene. HARSL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HARSL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HARSL BINDING SITE, designated SEQ ID:14509, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33330] Another function of VGAM877 is therefore inhibition of Histidyl-tRNA Synthetase-like (HARSL, Accession NM\_012208). Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HARSL. KIAA1939 (Accession NM\_024837) is another VGAM877 host target gene. KIAA1939 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1939, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of KIAA1939 BINDING SITE, designated SEQ ID:24243, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33331] Another function of VGAM877 is therefore inhibition of KIAA1939 (Accession NM\_024837). Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1939. LOC144699 (Accession XM\_084940) is another VGAM877 host target gene. LOC144699 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC144699, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144699 BINDING SITE, designated SEQ ID:37769, to the nucleotide sequence of VGAM877 RNA, herein designated VGAM RNA, also designated SEQ ID:3588.

[33332] Another function of VGAM877 is therefore inhibition of LOC144699 (Accession XM\_084940). Accordingly, utilities of VGAM877 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144699. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 878 (VGAM878) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33333] VGAM878 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM878 was detected is described hereinabove with reference to Figs. 1–8.

[33334] VGAM878 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Swinepox Virus. VGAM878 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33335] VGAM878 gene encodes a VGAM878 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM878 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM878 precursor RNA is designated SEQ ID:864, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:864 is



located at position 106591 relative to the genome of Swinepox Virus.

[33336] VGAM878 precursor RNA folds onto itself, forming VGAM878 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33337] An enzyme complex designated DICER COMPLEX, `dices` the VGAM878 folded precursor RNA into VGAM878 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM878 RNA is designated SEQ ID:3589, and is provided hereinbelow with reference to the sequence listing part.

[33338] VGAM878 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM878 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM878 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33339] VGAM878 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM878 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM878 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM878 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM878 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33340] The complementary binding of VGAM878 RNA, herein designated VGAM RNA, to host target binding sites on VGAM878 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM878 host target RNA into VGAM878 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33341] It is appreciated that VGAM878 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM878 host target genes. The mRNA of each one of this plurality of VGAM878 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM878 RNA, herein designated VGAM RNA, and which when bound by VGAM878 RNA causes inhibition of translation of respective one or more VGAM878

host target proteins.

[33342] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM878 gene, herein designated VGAM GENE, on one or more VGAM878 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33343] It is yet further appreciated that a function of VGAM878 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM878 include diagnosis, prevention and treatment of viral infection by Swinepox Virus. Specific

functions, and accordingly utilities, of VGAM878 correlate with, and may be deduced from, the identity of the host target genes which VGAM878 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33344] Nucleotide sequences of the VGAM878 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM878 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM878 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM878 are further described hereinbelow with reference to Table 1.

[33345] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM878 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM878 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33346] As mentioned hereinabove with reference to Fig. 1, a function of VGAM878 gene, herein designated VGAM is inhibition of expression of VGAM878 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM878 correlate with, and may be deduced from, the identity of the target genes which VGAM878 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33347] Protocadherin Beta 8 (PCDHB8, Accession NM\_019120) is a VGAM878 host target gene. PCDHB8 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PCDHB8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHB8 BINDING SITE, designated SEQ ID:21207, to the nucleotide sequence of VGAM878 RNA, herein designated VGAM RNA, also designated SEQ ID:3589.

[33348] A function of VGAM878 is therefore inhibition of Protocadherin Beta 8 (PCDHB8, Accession NM\_019120). Accordingly, utilities of VGAM878 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHB8. LOC145871 (Accession XM\_096897) is another VGAM878 host target gene. LOC145871 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC145871, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145871 BINDING SITE, designated SEQ ID:40622, to the nucleotide sequence of VGAM878 RNA, herein designated VGAM RNA, also designated SEQ ID:3589.

[33349] Another function of VGAM878 is therefore inhibition of LOC145871 (Accession XM\_096897). Accordingly, utilities of VGAM878 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145871. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 879 (VGAM879) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33350] VGAM879 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM879 was detected is described hereinabove with reference to Figs. 1–8.

[33351] VGAM879 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Amsacta Moorei Ento–

mopoxvirus. VGAM879 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33352] VGAM879 gene encodes a VGAM879 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM879 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM879 precursor RNA is designated SEQ ID:865, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:865 is located at position 137324 relative to the genome of Am-sacta Moorei Entomopoxvirus.

[33353] VGAM879 precursor RNA folds onto itself, forming VGAM879 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33354] An enzyme complex designated DICER COMPLEX, `dices`



the VGAM879 folded precursor RNA into VGAM879 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM879 RNA is designated SEQ ID:3590, and is provided hereinbelow with reference to the sequence listing part.

[33355] VGAM879 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM879 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM879 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33356] VGAM879 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM879 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM879 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM879 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM879 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33357] The complementary binding of VGAM879 RNA, herein designated VGAM RNA, to host target binding sites on VGAM879 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM879 host target RNA into VGAM879 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33358] It is appreciated that VGAM879 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM879 host target genes. The mRNA of each one of this plurality of VGAM879 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM879 RNA, herein designated VGAM RNA, and which when bound by VGAM879 RNA causes inhibition of translation of respective one or more VGAM879 host target proteins.

[33359] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM879 gene, herein designated VGAM GENE, on one or more VGAM879 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33360] It is yet further appreciated that a function of VGAM879 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM879 include diagnosis, prevention and treatment of viral infection by Amsacta Moorei Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM879 correlate with, and may be deduced from, the identity of the host target genes which VGAM879 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33361] Nucleotide sequences of the VGAM879 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM879 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM879 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM879 are further described hereinbelow with reference to Table 1.

[33362] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM879 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM879 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33363] As mentioned hereinabove with reference to Fig. 1, a function of VGAM879 gene, herein designated VGAM is inhibition of expression of VGAM879 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM879 correlate with, and may be deduced from, the identity of the target genes which VGAM879 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33364] KIAA0256 (Accession XM\_034905) is a VGAM879 host target gene. KIAA0256 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0256, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0256 BINDING SITE, designated SEQ ID:32184, to the nucleotide sequence of

VGAM879 RNA, herein designated VGAM RNA, also designated SEQ ID:3590.

[33365] A function of VGAM879 is therefore inhibition of KIAA0256 (Accession XM\_034905). Accordingly, utilities of VGAM879 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0256. TOLLIP (Accession NM\_019009) is another VGAM879 host target gene. TOLLIP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TOLLIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOLLIP BINDING SITE, designated SEQ ID:21094, to the nucleotide sequence of VGAM879 RNA, herein designated VGAM RNA, also designated SEQ ID:3590.

[33366] Another function of VGAM879 is therefore inhibition of TOLLIP (Accession NM\_019009). Accordingly, utilities of VGAM879 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOLLIP. LOC133744 (Accession XM\_059669) is another VGAM879 host target gene. LOC133744 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of

mRNA encoded by LOC133744, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133744 BINDING SITE, designated SEQ ID:37059, to the nucleotide sequence of VGAM879 RNA, herein designated VGAM RNA, also designated SEQ ID:3590.

[33367] Another function of VGAM879 is therefore inhibition of LOC133744 (Accession XM\_059669). Accordingly, utilities of VGAM879 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133744. LOC203369 (Accession XM\_114689) is another VGAM879 host target gene. LOC203369 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203369, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203369 BINDING SITE, designated SEQ ID:43031, to the nucleotide sequence of VGAM879 RNA, herein designated VGAM RNA, also designated SEQ ID:3590.

[33368] Another function of VGAM879 is therefore inhibition of LOC203369 (Accession XM\_114689). Accordingly, utilities

of VGAM879 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203369. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 880 (VGAM880) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33369] VGAM880 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM880 was detected is described hereinabove with reference to Figs. 1–8.

[33370] VGAM880 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 3. VGAM880 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33371] VGAM880 gene encodes a VGAM880 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM880 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–



quence of VGAM880 precursor RNA is designated SEQ ID:866, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:866 is located at position 52351 relative to the genome of Gallid Herpesvirus 3.

[33372] VGAM880 precursor RNA folds onto itself, forming VGAM880 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33373] An enzyme complex designated DICER COMPLEX, `dices` the VGAM880 folded precursor RNA into VGAM880 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM880 RNA is designated SEQ ID:3591, and

is provided hereinbelow with reference to the sequence listing part.

[33374] VGAM880 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM880 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM880 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33375] VGAM880 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM880 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM880 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM880 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM880 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33376] The complementary binding of VGAM880 RNA, herein designated VGAM RNA, to host target binding sites on VGAM880 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM880 host target RNA into VGAM880 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33377] It is appreciated that VGAM880 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM880 host target genes. The mRNA of each one of this plurality of VGAM880 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM880 RNA, herein designated VGAM RNA, and which when bound by VGAM880 RNA causes inhibition of translation of respective one or more VGAM880 host target proteins.

[33378] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM880 gene, herein designated VGAM GENE, on one or more VGAM880 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33379] It is yet further appreciated that a function of VGAM880 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 3. Specific functions, and accordingly utilities, of VGAM880 correlate with, and may be deduced from, the identity of the host target genes which VGAM880 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33380] Nucleotide sequences of the VGAM880 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM880 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM880 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM880 are further described hereinbelow with reference to Table 1.

[33381] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM880 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM880 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33382] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM880 gene, herein designated VGAM is inhibition of expression of VGAM880 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM880 correlate with, and may be deduced from, the identity of the target genes which VGAM880 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33383] Chloride Channel, Calcium Activated, Family Member 3 (CLCA3, Accession NM\_004921) is a VGAM880 host target gene. CLCA3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLCA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLCA3 BINDING SITE, designated SEQ ID:11355, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33384] A function of VGAM880 is therefore inhibition of Chloride Channel, Calcium Activated, Family Member 3 (CLCA3, Accession NM\_004921), a gene which is similar to calcium-activated chloride channel family. Accordingly, utilities of VGAM880 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with CLCA3. The function of CLCA3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM595. Engulfment and Cell Motility 2 (ced-12 homolog, *C. elegans*) (ELMO2, Accession NM\_133171) is another VGAM880 host target gene. ELMO2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ELMO2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELMO2 BINDING SITE, designated SEQ ID:28394, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33385] Another function of VGAM880 is therefore inhibition of Engulfment and Cell Motility 2 (ced-12 homolog, *C. elegans*) (ELMO2, Accession NM\_133171). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELMO2. LFG (Accession XM\_084780) is another VGAM880 host target gene. LFG BINDING SITE is HOST TARGET bind-

ing site found in the 3` untranslated region of mRNA encoded by LFG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LFG BINDING SITE, designated SEQ ID:37690, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33386] Another function of VGAM880 is therefore inhibition of LFG (Accession XM\_084780). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LFG. Steroid-5-alpha-reductase, Alpha Polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) (SRD5A1, Accession NM\_001047) is another VGAM880 host target gene. SRD5A1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SRD5A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SRD5A1 BINDING SITE, designated SEQ ID:6717, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ



ID:3591.

[33387] Another function of VGAM880 is therefore inhibition of Steroid-5-alpha-reductase, Alpha Polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) (SRD5A1, Accession NM\_001047), a gene which catalyzes the conversion of testosterone into 5-alpha-dihydrotestosterone and progesterone . Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SRD5A1. The function of SRD5A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM749. Di-Ras2 (Accession NM\_017594) is another VGAM880 host target gene. Di-Ras2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by Di-Ras2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Di-Ras2 BINDING SITE, designated SEQ ID:19047, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33388] Another function of VGAM880 is therefore inhibition of

Di-Ras2 (Accession NM\_017594). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Di-Ras2. FLJ12700 (Accession NM\_024910) is another VGAM880 host target gene. FLJ12700 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12700 BINDING SITE, designated SEQ ID:24417, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33389] Another function of VGAM880 is therefore inhibition of FLJ12700 (Accession NM\_024910). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12700. KIAA0427 (Accession NM\_014772) is another VGAM880 host target gene. KIAA0427 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0427, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0427 BINDING SITE, designated SEQ ID:16581, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33390] Another function of VGAM880 is therefore inhibition of KIAA0427 (Accession NM\_014772). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0427. KIAA1223 (Accession XM\_048747) is another VGAM880 host target gene. KIAA1223 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1223, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1223 BINDING SITE, designated SEQ ID:35250, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33391] Another function of VGAM880 is therefore inhibition of KIAA1223 (Accession XM\_048747). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1223. KIAA1383 (Accession XM\_045859) is another

VGAM880 host target gene. KIAA1383 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1383, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1383 BINDING SITE, designated SEQ ID:34586, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33392] Another function of VGAM880 is therefore inhibition of KIAA1383 (Accession XM\_045859). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1383. KIAA1872 (Accession XM\_031917) is another VGAM880 host target gene. KIAA1872 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1872, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1872 BINDING SITE, designated SEQ ID:31524, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33393] Another function of VGAM880 is therefore inhibition of KIAA1872 (Accession XM\_031917). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1872. TAF2 RNA Polymerase II, TATA Box Binding Protein (TBP)–associated Factor, 150kDa (TAF2, Accession NM\_003184) is another VGAM880 host target gene. TAF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TAF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAF2 BINDING SITE, designated SEQ ID:9159, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33394] Another function of VGAM880 is therefore inhibition of TAF2 RNA Polymerase II, TATA Box Binding Protein (TBP)–associated Factor, 150kDa (TAF2, Accession NM\_003184). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAF2. LOC144262 (Accession XM\_084793) is another VGAM880 host target gene. LOC144262 BINDING SITE is HOST TARGET binding

site found in the 5` untranslated region of mRNA encoded by LOC144262, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC144262 BINDING SITE, designated SEQ ID:37706, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33395] Another function of VGAM880 is therefore inhibition of LOC144262 (Accession XM\_084793). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC144262. LOC149103 (Accession XM\_086434) is another VGAM880 host target gene. LOC149103 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC149103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149103 BINDING SITE, designated SEQ ID:38650, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33396] Another function of VGAM880 is therefore inhibition of

LOC149103 (Accession XM\_086434). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149103. LOC199733 (Accession XM\_117123) is another VGAM880 host target gene. LOC199733 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199733, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199733 BINDING SITE, designated SEQ ID:43247, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33397] Another function of VGAM880 is therefore inhibition of LOC199733 (Accession XM\_117123). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199733. LOC253805 (Accession XM\_172854) is another VGAM880 host target gene. LOC253805 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253805, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC253805 BINDING SITE, designated SEQ ID:46132, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33398] Another function of VGAM880 is therefore inhibition of LOC253805 (Accession XM\_172854). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253805. LOC90321 (Accession XM\_030896) is another VGAM880 host target gene. LOC90321 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90321, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90321 BINDING SITE, designated SEQ ID:31211, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33399] Another function of VGAM880 is therefore inhibition of LOC90321 (Accession XM\_030896). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90321. LOC92249 (Accession XM\_043814) is another



VGAM880 host target gene. LOC92249 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92249, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92249 BINDING SITE, designated SEQ ID:34021, to the nucleotide sequence of VGAM880 RNA, herein designated VGAM RNA, also designated SEQ ID:3591.

[33400] Another function of VGAM880 is therefore inhibition of LOC92249 (Accession XM\_043814). Accordingly, utilities of VGAM880 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92249. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 881 (VGAM881) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33401] VGAM881 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM881 was detected is described

hereinabove with reference to Figs. 1–8.

[33402] VGAM881 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 3.

VGAM881 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33403] VGAM881 gene encodes a VGAM881 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM881 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM881 precursor RNA is designated SEQ ID:867, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:867 is located at position 51459 relative to the genome of Gallid Herpesvirus 3.

[33404] VGAM881 precursor RNA folds onto itself, forming VGAM881 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[33405] An enzyme complex designated DICER COMPLEX, `dices` the VGAM881 folded precursor RNA into VGAM881 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM881 RNA is designated SEQ ID:3592, and is provided hereinbelow with reference to the sequence listing part.

[33406] VGAM881 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM881 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM881 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33407] VGAM881 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM881 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM881 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM881 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM881 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33408] The complementary binding of VGAM881 RNA, herein designated VGAM RNA, to host target binding sites on VGAM881 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM881 host target RNA into VGAM881 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33409] It is appreciated that VGAM881 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM881 host target genes. The mRNA of each one of this plurality of VGAM881 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM881 RNA, herein designated VGAM RNA, and which when bound by VGAM881 RNA causes inhibition of translation of respective one or more VGAM881 host target proteins.

[33410] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM881 gene, herein designated VGAM GENE, on one or more VGAM881 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33411] It is yet further appreciated that a function of VGAM881 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 3. Specific functions, and accordingly utilities, of VGAM881 correlate with, and may be deduced from, the identity of the host target genes which VGAM881 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33412] Nucleotide sequences of the VGAM881 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM881 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM881 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM881 are further described hereinbelow with reference to Table 1.

[33413] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM881 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM881 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33414] As mentioned hereinabove with reference to Fig. 1, a function of VGAM881 gene, herein designated VGAM is inhibition of expression of VGAM881 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM881 correlate with, and may be deduced from, the identity of the target genes which VGAM881 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33415] Carnitine O-octanoyltransferase (CROT, Accession NM\_021151) is a VGAM881 host target gene. CROT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CROT, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CROT BINDING SITE, designated SEQ ID:22121, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33416] A function of VGAM881 is therefore inhibition of Carnitine O-octanoyltransferase (CROT, Accession NM\_021151), a gene which CROT plays a crucial role in the beta-oxidation of branched-chain fatty acids including pristanic acid. Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CROT. The function of CROT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM70. Dual Specificity Phosphatase 1 (DUSP1, Accession NM\_004417) is another VGAM881 host target gene. DUSP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DUSP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DUSP1 BINDING SITE, designated SEQ ID:10680, to the nucleotide sequence of



VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33417] Another function of VGAM881 is therefore inhibition of Dual Specificity Phosphatase 1 (DUSP1, Accession NM\_004417), a gene which is a dual specificity phosphatase . Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DUSP1. The function of DUSP1 has been established by previous studies. Keyse and Em-  
slie (1992) isolated and characterized a cDNA, which they designated CL100, corresponding to an mRNA that is highly inducible by oxidative stress and heat shock in human skin cells. The cDNA was obtained by differential screening of a library made from normal human skin fibroblasts stressed for 2 hours in a solution of hydrogen peroxide. The cDNA contains an open reading frame specifying a 367-residue protein of 39.3 kD predicted molecular mass with the structural features of a nonreceptor type protein-tyrosine phosphatase. It has significant amino acid sequence similarity to a tyr/ser-protein phosphatase encoded by the late gene H1 of vaccinia virus. The purified protein encoded by the open reading frame expressed in bacteria has intrinsic phosphatase ac-

tivity. Given the relationship between the levels of protein-tyrosine phosphorylation, receptor activity, cellular proliferation, and cell cycle control, Keyse and Emslie (1992) concluded that induction of this gene may play an important regulatory role in the human cellular response to environmental stress. Brondello et al. (1999) determined that DUSP1, which they called MKP1, is a labile protein with a half-life of approximately 45 minutes in CCL39 hamster fibroblasts. Its degradation was attenuated by inhibitors of the ubiquitin-directed proteasome complex. MKP1 was a target in vivo and in vitro for p42MAPK (OMIM Ref. No. 176948) or p44MAPK (OMIM Ref. No. 601795), which phosphorylates MKP1 on 2 C-terminal serine residues, ser359 and ser364. This phosphorylation did not modify MKP1's intrinsic ability to dephosphorylate p44MAPK, but led to stabilization of the protein. Brondello et al. (1999) concluded that these results illustrated the importance of regulated protein degradation in the control of mitogenic signaling.

[33418] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33419] Brondello, J.-M.; Pouyssegur, J.; McKenzie, F. R. : Reduced

MAP kinase phosphatase-1 degradation after p42/p44(MAPK)-dependent phosphorylation. Science 286: 2514-2517, 1999. ; and

[33420] Keyse, S. M.; Emslie, E. A. : Oxidative stress and heat shock induce a human gene encoding a protein-tyrosine phosphatase. Nature 359: 644-647, 1992.

[33421] Further studies establishing the function and utilities of DUSP1 are found in John Hopkins OMIM database record ID 600714, and in cited publications numbered 1005 and 10052-10055 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. HUS1 Checkpoint Homolog (*S. pombe*) (HUS1, Accession XM\_165873) is another VGAM881 host target gene. HUS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HUS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HUS1 BINDING SITE, designated SEQ ID:43788, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33422] Another function of VGAM881 is therefore inhibition of HUS1 Checkpoint Homolog (*S. pombe*) (HUS1, Accession

XM\_165873), a gene which May form DNA damage–responsive protein complex . Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HUS1. The function of HUS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM228. Muscleblind–like (Drosophila) (MBNL, Accession NM\_021038) is another VGAM881 host target gene. MBNL BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MBNL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MBNL BINDING SITE, designated SEQ ID:22024, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33423] Another function of VGAM881 is therefore inhibition of Muscleblind–like (Drosophila) (MBNL, Accession NM\_021038), a gene which binds to cug triplet repeat expansion dsrna (by similarity). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MBNL.

The function of MBNL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM95.FIBL-6 (Accession XM\_053531) is another VGAM881 host target gene. FIBL-6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FIBL-6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FIBL-6 BINDING SITE, designated SEQ ID:36099, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33424] Another function of VGAM881 is therefore inhibition of FIBL-6 (Accession XM\_053531). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FIBL-6. FLJ30046 (Accession NM\_144595) is another VGAM881 host target gene. FLJ30046 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ30046, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ30046 BINDING SITE, designated SEQ ID:29410, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33425] Another function of VGAM881 is therefore inhibition of FLJ30046 (Accession NM\_144595). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ30046. G Protein-coupled Receptor 105 (GPR105, Accession NM\_014879) is another VGAM881 host target gene. GPR105 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR105, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR105 BINDING SITE, designated SEQ ID:17022, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33426] Another function of VGAM881 is therefore inhibition of G Protein-coupled Receptor 105 (GPR105, Accession NM\_014879). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with GPR105. KIAA0261 (Accession XM\_042946) is another VGAM881 host target gene. KIAA0261 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0261, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0261 BINDING SITE, designated SEQ ID:33829, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33427] Another function of VGAM881 is therefore inhibition of KIAA0261 (Accession XM\_042946). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0261. KIAA1143 (Accession XM\_044014) is another VGAM881 host target gene. KIAA1143 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1143, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1143 BINDING SITE, designated SEQ ID:34069, to the

nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33428] Another function of VGAM881 is therefore inhibition of KIAA1143 (Accession XM\_044014). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1143. Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession NM\_033285) is another VGAM881 host target gene. TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TP53INP1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TP53INP1 BINDING SITE1 and TP53INP1 BINDING SITE2, designated SEQ ID:27109 and SEQ ID:36118 respectively, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33429] Another function of VGAM881 is therefore inhibition of Tumor Protein P53 Inducible Nuclear Protein 1 (TP53INP1, Accession NM\_033285). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TP53INP1.



LOC203305 (Accession XM\_117529) is another VGAM881 host target gene. LOC203305 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203305, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203305 BINDING SITE, designated SEQ ID:43509, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33430] Another function of VGAM881 is therefore inhibition of LOC203305 (Accession XM\_117529). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC203305. LOC254243 (Accession XM\_173233) is another VGAM881 host target gene. LOC254243 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254243, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254243 BINDING SITE, designated SEQ ID:46511, to the nucleotide sequence of VGAM881 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3592.

[33431] Another function of VGAM881 is therefore inhibition of LOC254243 (Accession XM\_173233). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254243. LOC90038 (Accession XM\_028305) is another VGAM881 host target gene. LOC90038 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90038 BINDING SITE, designated SEQ ID:30648, to the nucleotide sequence of VGAM881 RNA, herein designated VGAM RNA, also designated SEQ ID:3592.

[33432] Another function of VGAM881 is therefore inhibition of LOC90038 (Accession XM\_028305). Accordingly, utilities of VGAM881 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90038. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 882 (VGAM882) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33433] VGAM882 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM882 was detected is described hereinabove with reference to Figs. 1–8.

[33434] VGAM882 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Meleagrid Herpesvirus 1. VGAM882 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33435] VGAM882 gene encodes a VGAM882 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM882 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM882 precursor RNA is designated SEQ ID:868, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:868 is located at position 13598 relative to the genome of Meleagrid Herpesvirus 1.

[33436] VGAM882 precursor RNA folds onto itself, forming

VGAM882 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33437] An enzyme complex designated DICER COMPLEX, `dices` the VGAM882 folded precursor RNA into VGAM882 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 79%) nucleotide sequence of VGAM882 RNA is designated SEQ ID:3593, and is provided hereinbelow with reference to the sequence listing part.

[33438] VGAM882 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM882 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM882 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33439] VGAM882 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM882 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM882 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM882 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM882 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example

only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33440] The complementary binding of VGAM882 RNA, herein designated VGAM RNA, to host target binding sites on VGAM882 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM882 host target RNA into VGAM882 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33441] It is appreciated that VGAM882 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM882 host target genes. The mRNA of each one of this plurality of VGAM882 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM882 RNA, herein designated VGAM RNA, and which when bound by VGAM882 RNA causes inhibition of translation of respective one or more VGAM882 host target proteins.

[33442] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM882 gene, herein designated VGAM GENE, on one or more VGAM882 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33443] It is yet further appreciated that a function of VGAM882 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of viral infection by Meleagrid Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM882 correlate with, and may be deduced from, the identity of the host target genes which VGAM882 binds and inhibits,

and the function of these host target genes, as elaborated hereinbelow.

[33444] Nucleotide sequences of the VGAM882 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM882 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM882 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM882 are further described hereinbelow with reference to Table 1.

[33445] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM882 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM882 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33446] As mentioned hereinabove with reference to Fig. 1, a function of VGAM882 gene, herein designated VGAM is inhibition of expression of VGAM882 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM882 correlate with, and may be deduced from, the identity of the target genes which VGAM882 binds and inhibits, and the function of these target genes,



as elaborated hereinbelow.

[33447] Arginine Vasopressin Receptor 1A (AVPR1A, Accession NM\_000706) is a VGAM882 host target gene. AVPR1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AVPR1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AVPR1A BINDING SITE, designated SEQ ID:6373, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33448] A function of VGAM882 is therefore inhibition of Arginine Vasopressin Receptor 1A (AVPR1A, Accession NM\_000706), a gene which mediates cell contraction and proliferation, platelet aggregation, release of coagulation factor, and glycogenolysis. Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AVPR1A. The function of AVPR1A and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM549.EGF-like-domain, Multiple 5 (EGFL5, Accession XM\_098838) is another VGAM882 host target gene.

EGFL5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EGFL5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EGFL5 BINDING SITE, designated SEQ ID:41885, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33449] Another function of VGAM882 is therefore inhibition of EGF-like-domain, Multiple 5 (EGFL5, Accession XM\_098838). Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EGFL5. Eukaryotic Translation Initiation Factor 3, Subunit 10 Theta, 150/170kDa (EIF3S10, Accession XM\_049795) is another VGAM882 host target gene. EIF3S10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EIF3S10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EIF3S10 BINDING SITE, designated SEQ ID:35501, to the nucleotide sequence of

VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33450] Another function of VGAM882 is therefore inhibition of Eukaryotic Translation Initiation Factor 3, Subunit 10 Theta, 150/170kDa (EIF3S10, Accession XM\_049795), a gene which binds to the 40s ribosome and promotes the binding of methionyl-trnai and mrna. Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EIF3S10. The function of EIF3S10 has been established by previous studies. Eukaryotic translation initiation factors (EIFs) initiate protein synthesis from mRNAs. EIF3, at 650 kD, is the largest of the EIFs. According to Johnson et al. (1997), EIF3 has been implicated in several roles, including binding to the 40S ribosomal subunit and to other EIFs, possibly to align the factors for initial binding to the 40S subunit and the subsequent identification of the AUG initiation codon. The EIF3 protein synthesis initiation factor is composed of at least 8 subunits, the largest of which is p180. Nagase et al. (1995) identified an open reading frame with significant homology to mouse centrosomin B. Nagase et al. (1995) noted that this clone, which they termed KIAA0139, was ubiquitously expressed and

contained 21 units of an unusual 10–amino acid repeat. The full–length cDNA was later cloned and characterized independently by Johnson et al. (1997) and Scholler and Kanner (1997). Johnson et al. (1997) used expression screening of a human liver cDNA library to isolate a clone, which they termed p180. The cDNA predicted a protein of 1,382 amino acids, which Johnson et al. (1997) identified as the human homolog of centrosomin, the large subunit of mouse eif3. Johnson et al. (1997) also showed that p180 has homologs in yeast, nematodes, and plants. Scholler and Kanner (1997) used expression screening of a human T–cell cDNA library to isolate a clone, termed p167 by them, that was nearly identical to that isolated by Johnson et al. (1997). Scholler and Kanner (1997) showed that p167 was a cytoplasmic protein that is not phosphorylated and is part of a multisubunit complex.

[33451] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33452] Johnson, K. R.; Merrick, W. C.; Zoll, W. L.; Zhu, Y. : Identification of cDNA clones for the large subunit of eukaryotic translation initiation factor 3: comparison of homologues from human, *Nicotiana tabacum*, *Caenorhabditis elegans*,

and *Saccharomyces cerevisiae*. J. Biol. Chem. 272:  
7106–7113, 1997. ; and

[33453] Scholler, J. K.; Kanner, S. B. : The human p167 gene encodes a unique structural protein that contains centrosomin A homology and associates with a multicomponent complex. DNA Cell Biol.

[33454] Further studies establishing the function and utilities of EIF3S10 are found in John Hopkins OMIM database record ID 602039, and in cited publications numbered 953–95 and 10969 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Nuclear Receptor Coactivator 6 (NCOA6, Accession NM\_014071) is another VGAM882 host target gene. NCOA6 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by NCOA6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA6 BINDING SITE, designated SEQ ID:15287, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33455] Another function of VGAM882 is therefore inhibition of Nuclear Receptor Coactivator 6 (NCOA6, Accession

NM\_014071), a gene which activates gene transcription through ligand-dependent association with coactivators. Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA6. The function of NCOA6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM25. Phenylalanine Hydroxylase (PAH, Accession NM\_000277) is another VGAM882 host target gene. PAH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAH BINDING SITE, designated SEQ ID:5822, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33456] Another function of VGAM882 is therefore inhibition of Phenylalanine Hydroxylase (PAH, Accession NM\_000277). Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAH. Tropomodulin (TMOD, Accession

NM\_003275) is another VGAM882 host target gene. TMOD BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TMOD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TMOD BINDING SITE, designated SEQ ID:9292, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33457] Another function of VGAM882 is therefore inhibition of Tropomodulin (TMOD, Accession NM\_003275), a gene which blocks the elongation and depolymerization of the actin filaments at the pointed end. Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TMOD. The function of TMOD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM716. Protocadherin 20 (PCDH20, Accession NM\_022843) is another VGAM882 host target gene. PCDH20 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PCDH20, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDH20 BINDING SITE, designated SEQ ID:23134, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33458] Another function of VGAM882 is therefore inhibition of Protocadherin 20 (PCDH20, Accession NM\_022843). Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDH20. Protein Phosphatase 1, Regulatory (inhibitor) Subunit 3B (PPP1R3B, Accession NM\_024607) is another VGAM882 host target gene. PPP1R3B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1R3B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R3B BINDING SITE, designated SEQ ID:23856, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33459] Another function of VGAM882 is therefore inhibition of Protein Phosphatase 1, Regulatory (inhibitor) Subunit 3B



(PPP1R3B, Accession NM\_024607). Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R3B. LOC151446 (Accession XM\_098061) is another VGAM882 host target gene. LOC151446 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151446, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151446 BINDING SITE, designated SEQ ID:41351, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33460] Another function of VGAM882 is therefore inhibition of LOC151446 (Accession XM\_098061). Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151446. LOC161823 (Accession XM\_091156) is another VGAM882 host target gene. LOC161823 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC161823, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC161823 BINDING SITE, designated SEQ ID:40031, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33461] Another function of VGAM882 is therefore inhibition of LOC161823 (Accession XM\_091156). Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161823. LOC221490 (Accession XM\_168084) is another VGAM882 host target gene. LOC221490 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221490, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221490 BINDING SITE, designated SEQ ID:44988, to the nucleotide sequence of VGAM882 RNA, herein designated VGAM RNA, also designated SEQ ID:3593.

[33462] Another function of VGAM882 is therefore inhibition of LOC221490 (Accession XM\_168084). Accordingly, utilities of VGAM882 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221490. Fig. 1 further provides a conceptual descrip-

tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 883 (VGAM883) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33463] VGAM883 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM883 was detected is described hereinabove with reference to Figs. 1–8.

[33464] VGAM883 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 3. VGAM883 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33465] VGAM883 gene encodes a VGAM883 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM883 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM883 precursor RNA is designated SEQ ID:869, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:869 is

located at position 33063 relative to the genome of Gallid Herpesvirus 3.

[33466] VGAM883 precursor RNA folds onto itself, forming VGAM883 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33467] An enzyme complex designated DICER COMPLEX, `dices` the VGAM883 folded precursor RNA into VGAM883 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 88%) nucleotide sequence of VGAM883 RNA is designated SEQ ID:3594, and is provided hereinbelow with reference to the sequence listing part.

[33468] VGAM883 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM883 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM883 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33469] VGAM883 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM883 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM883 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM883 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM883 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33470] The complementary binding of VGAM883 RNA, herein designated VGAM RNA, to host target binding sites on VGAM883 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM883 host target RNA into VGAM883 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33471] It is appreciated that VGAM883 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM883 host target genes. The mRNA of each one of this plurality of VGAM883 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM883 RNA, herein designated VGAM RNA, and which when bound by VGAM883 RNA causes inhibition of translation of respective one or more VGAM883

host target proteins.

[33472] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM883 gene, herein designated VGAM GENE, on one or more VGAM883 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33473] It is yet further appreciated that a function of VGAM883 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 3. Spe-

cific functions, and accordingly utilities, of VGAM883 correlate with, and may be deduced from, the identity of the host target genes which VGAM883 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33474] Nucleotide sequences of the VGAM883 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM883 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM883 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM883 are further described hereinbelow with reference to Table 1.

[33475] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM883 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM883 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33476] As mentioned hereinabove with reference to Fig. 1, a function of VGAM883 gene, herein designated VGAM is inhibition of expression of VGAM883 target genes. It is appreciated that specific functions, and accordingly utili-



ties, of VGAM883 correlate with, and may be deduced from, the identity of the target genes which VGAM883 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33477] Adenylate Cyclase 9 (ADCY9, Accession NM\_001116) is a VGAM883 host target gene. ADCY9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADCY9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADCY9 BINDING SITE, designated SEQ ID:6792, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33478] A function of VGAM883 is therefore inhibition of Adenylate Cyclase 9 (ADCY9, Accession NM\_001116), a gene which . may be a physiologically relevant docking site for calcineurin (by similarity). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADCY9. The function of ADCY9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference

to VGAM477.Discs, Large (Drosophila) Homolog 4 (DLG4, Accession NM\_001365) is another VGAM883 host target gene. DLG4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DLG4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DLG4 BINDING SITE, designated SEQ ID:7046, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33479] Another function of VGAM883 is therefore inhibition of Discs, Large (Drosophila) Homolog 4 (DLG4, Accession NM\_001365), a gene which is a membrane-associated guanylate kinase and may intervene in synaptogenesis. Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DLG4. The function of DLG4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM206.ELAV (embryonic lethal, abnormal vision, Drosophila)-like 3 (Hu antigen C) (ELAVL3, Accession NM\_001420) is another VGAM883 host target gene. ELAVL3 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by ELAVL3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELAVL3 BINDING SITE, designated SEQ ID:7120, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33480] Another function of VGAM883 is therefore inhibition of ELAV (embryonic lethal, abnormal vision, *Drosophila*)-like 3 (Hu antigen C) (ELAVL3, Accession NM\_001420), a gene which arises when an immune response to systemic tumors expressing neuronal proteins develops into an autoimmune neuronal degeneration. Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELAVL3. The function of ELAVL3 has been established by previous studies. Paraneoplastic neurologic disorders (PNDs) are a group of neurologic syndromes that arise when an immune response to systemic tumors expressing neuronal proteins develops into an autoimmune neuronal degeneration. Sakai et al. (1994) determined that the serum of a patient with paraneoplastic limbic encephalitis (PLE) con-

tained autoantibodies that recognized a 38-kD nuclear antigen in neural cells. By screening a hippocampus expression library with this serum, they isolated cDNAs encoding a protein that they called PLE21. The predicted 350-amino acid protein contains 3 RNA recognition motifs (RRMs). PLE21 shares 82% and 54% protein sequence identity with the human neural autoantigen HuD (OMIM Ref. No. 168360) and *Drosophila* ELAV protein, respectively. Northern blot analysis revealed that PLE21 is expressed as an approximately 2-kb mRNA exclusively in brain. Liu et al. (1995) stated that PLE21, or HuC, is one of several Hu antigens, neuronal-specific RNA-binding proteins recognized by the anti-Hu serum antibody present in sera from patients with paraneoplastic encephalomyelitis and sensory neuronopathy (PEM/PSN). The Hu antigens HuD, HuC, and Hel-N1 (OMIM Ref. No. 601673) each contain 2 tandemly arranged RRM connected to a third RRM by a highly basic segment. Abe et al. (1996) cloned cDNAs encoding mouse HuC. The predicted mouse and human proteins are 96% identical. These authors found that alternative splicing generates 2 mouse HuC isoforms, both of which can bind to AU-rich elements (AREs) within the 3-prime untranslated regions of mRNAs. Functional do-

main mapping using mouse HuC deletion mutants showed that the first RRM binds to ARE, that the second RRM has no binding activity by itself but facilitates ARE binding by the first RRM, and that the third RRM has specific binding activity for the poly(A) sequence. By fluorescence in situ hybridization (FISH), Van Tine et al. (1998) mapped the ELAVL3 gene to 19p13.2. Using FISH and radiation hybrid analysis, they demonstrated that ELAVL3 is centromeric to the ELAVL1 (HuR; 603466) gene located in the same chromosomal region. By analysis of an interspecific backcross, Fletcher et al. (1997) mapped the mouse HuC gene to chromosome 9, in a region showing homology of synteny to human chromosome 19p13.2.

[33481] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33482] Sakai, K.; Gofuku, M.; Kitagawa, Y.; Ogasawara, T.; Hirose, G.; Yamazaki, M.; Koh, C.-S.; Yanagisawa, N.; Steinman, L. : A hippocampal protein associated with paraneoplastic neurologic syndrome and small cell lung carcinoma. Biochem. Biophys. Res. Commun. 199: 1200–1208, 1994.  
; and

[33483] Van Tine, B. A.; Knops, J. F.; Butler, A.; Deloukas, P.; Shaw,

G. M.; King, P. H. : Localization of HuC (ELAVL3) to chromosome 19p13.2 by fluorescence in situ hybridization utilizing a n.

[33484] Further studies establishing the function and utilities of ELAVL3 are found in John Hopkins OMIM database record ID 603458, and in cited publications numbered 598 and 5833–5835 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Interleukin 1 Receptor, Type I (IL1R1, Accession NM\_000877) is another VGAM883 host target gene. IL1R1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL1R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL1R1 BINDING SITE, designated SEQ ID:6566, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33485] Another function of VGAM883 is therefore inhibition of Interleukin 1 Receptor, Type I (IL1R1, Accession NM\_000877), a gene which is a receptor for interleukin-1 alpha (il-1a), beta (il-1b), and interleukin-1 receptor antagonist protein (il-1ra). Accordingly, utilities of VGAM883

include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL1R1. The function of IL1R1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM704.LIM Homeobox Protein 5 (LHX5, Accession NM\_022363) is another VGAM883 host target gene. LHX5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LHX5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LHX5 BINDING SITE, designated SEQ ID:22750, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33486] Another function of VGAM883 is therefore inhibition of LIM Homeobox Protein 5 (LHX5, Accession NM\_022363). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LHX5. Microtubule-associated Protein, RP/EB Family, Member 3 (MAPRE3, Accession NM\_012326) is another VGAM883 host target gene. MAPRE3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated

region of mRNA encoded by MAPRE3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPRE3 BINDING SITE, designated SEQ ID:14712, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33487] Another function of VGAM883 is therefore inhibition of Microtubule-associated Protein, RP/EB Family, Member 3 (MAPRE3, Accession NM\_012326), a gene which interact with cytoplasmic microtubules, and with the adenomatous polyposis coli. Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPRE3. The function of MAPRE3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM340.V-rel Reticuloendotheliosis Viral Oncogene Homolog A, Nuclear Factor of Kappa Light Polypeptide Gene Enhancer In B-cells 3, P65 (avian) (RELA, Accession NM\_021975) is another VGAM883 host target gene. RELA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RELA, corre-



sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RELA BINDING SITE, designated SEQ ID:22500, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33488] Another function of VGAM883 is therefore inhibition of V-rel Reticuloendotheliosis Viral Oncogene Homolog A, Nuclear Factor of Kappa Light Polypeptide Gene Enhancer In B-cells 3, P65 (avian) (RELA, Accession NM\_021975), a gene which has a DNA-binding domain and regulates transcription as a heterodimer with NFKB1. Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RELA. The function of RELA has been established by previous studies. Jacobs and Harrison (1998) and Huxford et al. (1998) determined the structure of the NFKBIA ankyrin repeat domain, bound to a partially truncated NFKB heterodimer (p50/p65), by x-ray crystallography at 2.7- and 2.3-angstrom resolution, respectively. It shows a stack of 6 NFKBIA ankyrin repeats facing the C-terminal domains of the NFKB rel homology regions. Contacts occur in discontinuous patches, suggesting a combinatorial

quality for ankyrin repeat specificity. The first 2 repeats cover an alpha helically ordered segment containing the p65 nuclear localization signal. The position of the sixth ankyrin repeat shows that full-length NFKBIA will occlude the NFKB DNA-binding cleft. The orientation of NFKBIA in the complex places its N- and C-terminal regions in appropriate locations for their known regulatory functions. Baeuerle (1998) discussed the model of interactions between NFKBIA and NFKB. Animal model experiments lend further support to the function of RELA. Neurath et al. (1996) reported direct evidence for the involvement of p65 in chronic intestinal inflammation induced in mice and suggested a potential molecular therapeutic approach to the treatment of patients with Crohn disease (OMIM Ref. No. 266600) using p65 antisense oligonucleotides.

[33489] It is appreciated that the abovementioned animal model for RELA is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[33490] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33491] Baeuerle, P. A. : I-kappa-B--NF-kappa-B structures: at

the interface of inflammation control. Cell 95: 729–731, 1998. ; and

[33492] Neurath, M. F.; Pettersson, S.; Myer zum Buschenfelde, K.–H.; Strober, W. : Local administration of antisense phosphorothioate oligonucleotides to the p65 subunit of NF–kappa–B abrogate.

[33493] Further studies establishing the function and utilities of RELA are found in John Hopkins OMIM database record ID 164014, and in cited publications numbered 2244–1714, 3984–1716, 2245, 1273 and 12741 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Solute Carrier Family 5 (sodium iodide symporter), Member 5 (SLC5A5, Accession NM\_000453) is another VGAM883 host target gene. SLC5A5 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by SLC5A5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC5A5 BINDING SITE, designated SEQ ID:6068, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33494] Another function of VGAM883 is therefore inhibition of

Solute Carrier Family 5 (sodium iodide symporter), Member 5 (SLC5A5, Accession NM\_000453). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC5A5. Solute Carrier Family 6 (neurotransmitter transporter, creatine), Member 8 (SLC6A8, Accession NM\_005629) is another VGAM883 host target gene. SLC6A8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC6A8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC6A8 BINDING SITE, designated SEQ ID:12148, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33495] Another function of VGAM883 is therefore inhibition of Solute Carrier Family 6 (neurotransmitter transporter, creatine), Member 8 (SLC6A8, Accession NM\_005629). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC6A8. Cyclin M3 (CNNM3, Accession NM\_017623) is another VGAM883 host target gene.

CNNM3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CNNM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CNNM3 BINDING SITE, designated SEQ ID:19123, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33496] Another function of VGAM883 is therefore inhibition of Cyclin M3 (CNNM3, Accession NM\_017623). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CNNM3. DKFZp761F2014 (Accession NM\_020215) is another VGAM883 host target gene. DKFZp761F2014 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp761F2014, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp761F2014 BINDING SITE, designated SEQ ID:21459, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3594.

[33497] Another function of VGAM883 is therefore inhibition of DKFZp761F2014 (Accession NM\_020215). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp761F2014. ELL2 (Accession NM\_012081) is another VGAM883 host target gene. ELL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ELL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ELL2 BINDING SITE, designated SEQ ID:14367, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33498] Another function of VGAM883 is therefore inhibition of ELL2 (Accession NM\_012081). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ELL2. FLJ10315 (Accession NM\_018056) is another VGAM883 host target gene. FLJ10315 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ10315, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10315 BINDING SITE, designated SEQ ID:19818, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33499] Another function of VGAM883 is therefore inhibition of FLJ10315 (Accession NM\_018056). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10315. FLJ32865 (Accession NM\_144613) is another VGAM883 host target gene. FLJ32865 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ32865, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32865 BINDING SITE, designated SEQ ID:29427, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33500] Another function of VGAM883 is therefore inhibition of FLJ32865 (Accession NM\_144613). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with FLJ32865. Integrin, Alpha 10 (ITGA10, Accession XM\_002097) is another VGAM883 host target gene. ITGA10 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ITGA10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGA10 BINDING SITE, designated SEQ ID:29860, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33501] Another function of VGAM883 is therefore inhibition of Integrin, Alpha 10 (ITGA10, Accession XM\_002097). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGA10. KIAA0211 (Accession NM\_014630) is another VGAM883 host target gene. KIAA0211 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA0211, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0211 BINDING SITE, designated SEQ ID:15992, to the



nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33502] Another function of VGAM883 is therefore inhibition of KIAA0211 (Accession NM\_014630). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0211. KIAA0552 (Accession NM\_014731) is another VGAM883 host target gene. KIAA0552 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0552, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0552 BINDING SITE, designated SEQ ID:16344, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33503] Another function of VGAM883 is therefore inhibition of KIAA0552 (Accession NM\_014731). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0552. KIAA1111 (Accession XM\_171233) is another VGAM883 host target gene. KIAA1111 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1111, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1111 BINDING SITE, designated SEQ ID:46020, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33504] Another function of VGAM883 is therefore inhibition of KIAA1111 (Accession XM\_171233). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1111. KIAA1196 (Accession XM\_028968) is another VGAM883 host target gene. KIAA1196 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1196 BINDING SITE, designated SEQ ID:30817, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33505] Another function of VGAM883 is therefore inhibition of KIAA1196 (Accession XM\_028968). Accordingly, utilities

of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1196. KIAA1750 (Accession XM\_043067) is another VGAM883 host target gene. KIAA1750 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1750, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1750 BINDING SITE, designated SEQ ID:33874, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33506] Another function of VGAM883 is therefore inhibition of KIAA1750 (Accession XM\_043067). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1750. KIAA1755 (Accession XM\_028810) is another VGAM883 host target gene. KIAA1755 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1755, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1755 BINDING SITE, designated SEQ ID:30750, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33507] Another function of VGAM883 is therefore inhibition of KIAA1755 (Accession XM\_028810). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1755. KIAA1910 (Accession XM\_055514) is another VGAM883 host target gene. KIAA1910 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1910, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1910 BINDING SITE, designated SEQ ID:36287, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33508] Another function of VGAM883 is therefore inhibition of KIAA1910 (Accession XM\_055514). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1910. Leucine Rich Repeat (in FLII) Interacting Protein 1 (LRRFIP1, Accession NM\_004735) is another VGAM883

host target gene. LRRFIP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LRRFIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRRFIP1 BINDING SITE, designated SEQ ID:11119, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33509] Another function of VGAM883 is therefore inhibition of Leucine Rich Repeat (in FLII) Interacting Protein 1 (LRRFIP1, Accession NM\_004735). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRRFIP1. MFN2 (Accession NM\_014874) is another VGAM883 host target gene. MFN2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MFN2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MFN2 BINDING SITE, designated SEQ ID:17010, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33510] Another function of VGAM883 is therefore inhibition of MFN2 (Accession NM\_014874). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MFN2. MGC20255 (Accession NM\_052848) is another VGAM883 host target gene. MGC20255 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC20255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC20255 BINDING SITE, designated SEQ ID:27428, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33511] Another function of VGAM883 is therefore inhibition of MGC20255 (Accession NM\_052848). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC20255. Neuritin 1 (NRN1, Accession NM\_016588) is another VGAM883 host target gene. NRN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NRN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRN1 BINDING SITE, designated SEQ ID:18663, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33512] Another function of VGAM883 is therefore inhibition of Neuritin 1 (NRN1, Accession NM\_016588). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRN1. Protein Phosphatase 1, Regulatory (inhibitor) Subunit 1A (PPP1R1A, Accession NM\_006741) is another VGAM883 host target gene. PPP1R1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPP1R1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP1R1A BINDING SITE, designated SEQ ID:13591, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33513] Another function of VGAM883 is therefore inhibition of Protein Phosphatase 1, Regulatory (inhibitor) Subunit 1A (PPP1R1A, Accession NM\_006741). Accordingly, utilities of

VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP1R1A. RAB10, Member RAS Oncogene Family (RAB10, Accession XM\_097979) is another VGAM883 host target gene. RAB10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAB10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAB10 BINDING SITE, designated SEQ ID:41279, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33514] Another function of VGAM883 is therefore inhibition of RAB10, Member RAS Oncogene Family (RAB10, Accession XM\_097979). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAB10. LOC116113 (Accession XM\_166413) is another VGAM883 host target gene. LOC116113 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC116113, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-



cleotide sequences of LOC116113 BINDING SITE, designated SEQ ID:44285, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33515] Another function of VGAM883 is therefore inhibition of LOC116113 (Accession XM\_166413). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC116113. LOC146488 (Accession XM\_047748) is another VGAM883 host target gene. LOC146488 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146488, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146488 BINDING SITE, designated SEQ ID:35044, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33516] Another function of VGAM883 is therefore inhibition of LOC146488 (Accession XM\_047748). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146488. LOC149577 (Accession XM\_097675) is an-

other VGAM883 host target gene. LOC149577 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149577, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149577 BINDING SITE, designated SEQ ID:41022, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33517] Another function of VGAM883 is therefore inhibition of LOC149577 (Accession XM\_097675). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149577. LOC158310 (Accession XM\_098919) is another VGAM883 host target gene. LOC158310 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158310, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158310 BINDING SITE, designated SEQ ID:41949, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33518] Another function of VGAM883 is therefore inhibition of LOC158310 (Accession XM\_098919). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158310. LOC196500 (Accession XM\_113734) is another VGAM883 host target gene. LOC196500 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC196500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196500 BINDING SITE, designated SEQ ID:42389, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33519] Another function of VGAM883 is therefore inhibition of LOC196500 (Accession XM\_113734). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196500. LOC201475 (Accession XM\_113967) is another VGAM883 host target gene. LOC201475 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC201475, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC201475 BINDING SITE, designated SEQ ID:42578, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33520] Another function of VGAM883 is therefore inhibition of LOC201475 (Accession XM\_113967). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC201475. LOC253216 (Accession XM\_170765) is another VGAM883 host target gene. LOC253216 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253216, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253216 BINDING SITE, designated SEQ ID:45519, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33521] Another function of VGAM883 is therefore inhibition of LOC253216 (Accession XM\_170765). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC253216. LOC253868 (Accession XM\_170975) is another VGAM883 host target gene. LOC253868 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253868, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253868 BINDING SITE, designated SEQ ID:45747, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33522] Another function of VGAM883 is therefore inhibition of LOC253868 (Accession XM\_170975). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253868. LOC90019 (Accession NM\_138567) is another VGAM883 host target gene. LOC90019 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90019, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90019 BINDING SITE, designated SEQ ID:28871, to the nucleotide sequence of VGAM883 RNA, herein designated

VGAM RNA, also designated SEQ ID:3594.

[33523] Another function of VGAM883 is therefore inhibition of LOC90019 (Accession NM\_138567). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90019. LOC91397 (Accession XM\_038219) is another VGAM883 host target gene. LOC91397 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC91397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91397 BINDING SITE, designated SEQ ID:32782, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33524] Another function of VGAM883 is therefore inhibition of LOC91397 (Accession XM\_038219). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91397. LOC95702 (Accession XM\_031446) is another VGAM883 host target gene. LOC95702 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC95702, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC95702 BINDING SITE, designated SEQ ID:31382, to the nucleotide sequence of VGAM883 RNA, herein designated VGAM RNA, also designated SEQ ID:3594.

[33525] Another function of VGAM883 is therefore inhibition of LOC95702 (Accession XM\_031446). Accordingly, utilities of VGAM883 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC95702. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 884 (VGAM884) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33526] VGAM884 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM884 was detected is described hereinabove with reference to Figs. 1–8.

[33527] VGAM884 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Rat Cytomegalovirus.

VGAM884 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33528] VGAM884 gene encodes a VGAM884 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM884 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM884 precursor RNA is designated SEQ ID:870, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:870 is located at position 93181 relative to the genome of Rat Cytomegalovirus.

[33529] VGAM884 precursor RNA folds onto itself, forming VGAM884 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33530] An enzyme complex designated DICER COMPLEX, `dices`



the VGAM884 folded precursor RNA into VGAM884 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM884 RNA is designated SEQ ID:3595, and is provided hereinbelow with reference to the sequence listing part.

[33531] VGAM884 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM884 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM884 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33532] VGAM884 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM884 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM884 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM884 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM884 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[33533] The complementary binding of VGAM884 RNA, herein designated VGAM RNA, to host target binding sites on VGAM884 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM884 host target RNA into VGAM884 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33534] It is appreciated that VGAM884 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM884 host target genes. The mRNA of each one of this plurality of VGAM884 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM884 RNA, herein designated VGAM RNA, and which when bound by VGAM884 RNA causes inhibition of translation of respective one or more VGAM884 host target proteins.

[33535] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM884 gene, herein designated VGAM GENE, on one or more VGAM884 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33536] It is yet further appreciated that a function of VGAM884 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM884 include diagnosis, prevention and treatment of viral infection by Rat Cytomegalovirus. Specific functions, and accordingly utilities, of VGAM884 correlate with, and may be deduced from, the identity of the host target genes which VGAM884 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33537] Nucleotide sequences of the VGAM884 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM884 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM884 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM884 are further described hereinbelow with reference to Table 1.

[33538] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM884 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM884 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33539] As mentioned hereinabove with reference to Fig. 1, a function of VGAM884 gene, herein designated VGAM is inhibition of expression of VGAM884 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM884 correlate with, and may be deduced from, the identity of the target genes which VGAM884 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33540] Mitogen-activated Protein Kinase 1 (MAPK1, Accession NM\_002745) is a VGAM884 host target gene. MAPK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAPK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPK1 BINDING SITE, designated SEQ ID:8617, to the

nucleotide sequence of VGAM884 RNA, herein designated VGAM RNA, also designated SEQ ID:3595.

[33541] A function of VGAM884 is therefore inhibition of Mitogen-activated Protein Kinase 1 (MAPK1, Accession NM\_002745), a gene which phosphorylates microtubule-associated protein-2 (map2). myelin basic protein (mbp), and elk-1; may promote entry in the cell cycle. Accordingly, utilities of VGAM884 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPK1. The function of MAPK1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM217.LOC126302 (Accession XM\_059020) is another VGAM884 host target gene. LOC126302 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC126302, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC126302 BINDING SITE, designated SEQ ID:36825, to the nucleotide sequence of VGAM884 RNA, herein designated VGAM RNA, also designated SEQ ID:3595.

[33542] Another function of VGAM884 is therefore inhibition of LOC126302 (Accession XM\_059020). Accordingly, utilities of VGAM884 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126302. LOC51277 (Accession XM\_087054) is another VGAM884 host target gene. LOC51277 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC51277, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51277 BINDING SITE, designated SEQ ID:39023, to the nucleotide sequence of VGAM884 RNA, herein designated VGAM RNA, also designated SEQ ID:3595.

[33543] Another function of VGAM884 is therefore inhibition of LOC51277 (Accession XM\_087054). Accordingly, utilities of VGAM884 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51277. LOC56965 (Accession NM\_020213) is another VGAM884 host target gene. LOC56965 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC56965, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC56965 BINDING SITE, designated SEQ ID:21450, to the nucleotide sequence of VGAM884 RNA, herein designated VGAM RNA, also designated SEQ ID:3595.

[33544] Another function of VGAM884 is therefore inhibition of LOC56965 (Accession NM\_020213). Accordingly, utilities of VGAM884 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC56965. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 885 (VGAM885) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33545] VGAM885 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM885 was detected is described hereinabove with reference to Figs. 1–8.

[33546] VGAM885 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Adenovirus E. VGAM885 host target gene, herein designated VGAM



HOST TARGET GENE, is a human gene contained in the human genome.

[33547] VGAM885 gene encodes a VGAM885 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM885 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM885 precursor RNA is designated SEQ ID:871, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:871 is located at position 7211 relative to the genome of Human Adenovirus E.

[33548] VGAM885 precursor RNA folds onto itself, forming VGAM885 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33549] An enzyme complex designated DICER COMPLEX, `dices` the VGAM885 folded precursor RNA into VGAM885 RNA,

herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 73%) nucleotide sequence of VGAM885 RNA is designated SEQ ID:3596, and is provided hereinbelow with reference to the sequence listing part.

[33550] VGAM885 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM885 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM885 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33551] VGAM885 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM885 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM885 RNA is an accurate or a

partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM885 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM885 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33552] The complementary binding of VGAM885 RNA, herein designated VGAM RNA, to host target binding sites on VGAM885 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM885 host target RNA into VGAM885 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target

protein is therefore outlined by a broken line.

[33553] It is appreciated that VGAM885 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM885 host target genes. The mRNA of each one of this plurality of VGAM885 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM885 RNA, herein designated VGAM RNA, and which when bound by VGAM885 RNA causes inhibition of translation of respective one or more VGAM885 host target proteins.

[33554] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM885 gene, herein designated VGAM GENE, on one or more VGAM885 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate ex-

pression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33555] It is yet further appreciated that a function of VGAM885 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of viral infection by Human Adenovirus E. Specific functions, and accordingly utilities, of VGAM885 correlate with, and may be deduced from, the identity of the host target genes which VGAM885 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33556] Nucleotide sequences of the VGAM885 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM885 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM885 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM885 are further described hereinbelow with reference to Table 1.

[33557] Nucleotide sequences of host target binding sites, such as

BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM885 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM885 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33558] As mentioned hereinabove with reference to Fig. 1, a function of VGAM885 gene, herein designated VGAM is inhibition of expression of VGAM885 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM885 correlate with, and may be deduced from, the identity of the target genes which VGAM885 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33559] Alkaline Phosphatase, Intestinal (ALPI, Accession NM\_001631) is a VGAM885 host target gene. ALPI BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ALPI, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ALPI BINDING SITE, designated SEQ ID:7344, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM

RNA, also designated SEQ ID:3596.

[33560] A function of VGAM885 is therefore inhibition of Alkaline Phosphatase, Intestinal (ALPI, Accession NM\_001631), a gene which is a glycoprotein phosphatase. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ALPI. The function of ALPI has been established by previous studies. Harris et al. (1974) found no genetic variants by electrophoretic means. Lehmann (1980) provided biochemical corroboration of the genetic distinctness of 3 alkaline phosphatases: intestinal, placental, and liver/bone/kidney. The existence of at least 1 gene coding for the intestinal forms (adult and fetal), independent of the other forms listed here, is inescapable (Goldstein et al., 1980). Gogolin et al. (1982) found a monoclonal antibody raised against purified human placental alkaline phosphatase that crossreacted with the adult and fetal forms of intestinal alkaline phosphatase, despite the fact that the placental and intestinal enzymes are nonallelic. Berger et al. (1987) used alkaline phosphatase cDNA as a probe to clone intestinal alkaline phosphatase cDNA, since partial protein sequence data indicated a high degree of homology between intestinal alkaline phosphatase and the

reported sequence of the placental isoenzyme. Intestinal alkaline phosphatase cDNA, which is 3.1 kb, is somewhat larger than the cDNA for the placental isoenzyme, which is 2.8 kb. Differences and similarities were pointed out.

Henthorn et al. (1987) isolated and sequenced a cDNA that encodes the alkaline phosphatase expressed in adult human intestine and compared the sequence with those previously determined for the placental (OMIM Ref. No. 171800) and liver/bone/kidney (OMIM Ref. No. 171760) cDNAs. The deduced polypeptide showed 86.5% amino acid identity to placental ALP and 56.6% amino acid identity to liver/bone/kidney ALP. Thus, the immunologic cross-reactivity of ALPI and ALPP is perhaps explained.

Henthorn et al. (1988) isolated and sequenced the ALPI gene in its entirety. The gene is composed of 11 exons interrupted by 10 introns. Introns in intestinal, placental, and liver/bone/kidney ALP genes occur at analogous positions, confirming that these genes arose from a single ancestral gene. Henthorn et al. (1987) stated that the placental and intestinal ALP genes map to the same region of chromosome 2. Griffin et al. (1987) mapped both the placental and the intestinal alkaline phosphatase genes to 2q34–q37 by chromosomal in situ hybridization and hy-



bridization to the DNA of somatic cell hybrids. By fluorescence in situ hybridization, Wu et al. (1993) mapped ALPI to 2q36.3–q37.1. Pasteris et al. (1993) concluded from a molecular analysis of a chromosome 2 deletion mapping panel that the ALPI gene is on the telomeric side of both PAX3 (OMIM Ref. No. 606597) and COL4A3 (OMIM Ref. No. 120070) and close to CHRND (OMIM Ref. No. 100720).

[33561] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33562] Henthorn, P. S.; Raducha, M.; Edwards, Y. H.; Weiss, M. J.; Slaughter, C.; Lafferty, M. A.; Harris, H. : Nucleotide and amino acid sequences of human intestinal alkaline phosphatase: close homology to placental alkaline phosphatase. Proc. Nat. Acad. Sci. 84: 1234–1238, 1987. ; and

[33563] Langman, M. J. S.; Leuthold, E.; Robson, E. B.; Harris, J.; Luffman, J. E.; Harris, H. : Influence of diet on the 'intestinal' component of serum alkaline phosphatase in people of differ.

[33564] Further studies establishing the function and utilities of ALPI are found in John Hopkins OMIM database record ID 171740, and in cited publications numbered 10, 2495–2498, 1886, 2499–250 and 4112 listed in the bibli–

ography section hereinbelow, which are also hereby incorporated by reference. Ras Homolog Gene Family, Member C (ARHC, Accession NM\_005167) is another VGAM885 host target gene. ARHC BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ARHC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHC BINDING SITE, designated SEQ ID:11664, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33565] Another function of VGAM885 is therefore inhibition of Ras Homolog Gene Family, Member C (ARHC, Accession NM\_005167), a gene which remodels of the actin cytoskeleton during cell morphogenesis and motility. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHC. The function of ARHC has been established by previous studies. The small guanosine triphosphatase Rho regulates remodeling of the actin cytoskeleton during cell morphogenesis and motility. In their Figure 3C, Maekawa et al. (1999) diagrammed pro-

posed signaling pathways for Rho-induced remodeling of the actin cytoskeleton. They demonstrated that active Rho signals to its downstream effector ROCK (OMIM Ref. No. 601702), which phosphorylates and activates LIM kinase (see OMIM Ref. No. 601329). LIM kinase, in turn, phosphorylates cofilin (OMIM Ref. No. 601442), inhibiting its actin-depolymerizing activity. Clark et al. (2000) used an in vivo selection scheme to select highly metastatic melanoma cells. By analyzing these cells on DNA arrays, they defined a pattern of gene expression that correlates with progression to a metastatic phenotype. In particular, Clark et al. (2000) showed enhanced expression of several genes involved in extracellular matrix assembly and of a second set of genes that regulate, either directly or indirectly, the actin-based cytoskeleton. Clark et al. (2000) found that RhoC enhances metastasis when overexpressed, whereas a dominant-negative Rho inhibits metastasis. Analysis of the phenotype of cells expressing dominant-negative Rho or RhoC indicates that RhoC is important in tumor cell invasion. The genomic approach allowed Clark et al. (2000) to identify families of genes involved in a process, not just single genes, and could indicate which molecular and cellular events might be impor-

tant in complex biologic processes such as metastasis.

[33566] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33567] Clark, E. A.; Golub, T. R.; Lander, E. S.; Hynes, R. O. : Genomic analysis of metastasis reveals an essential role for RhoC. Nature 406: 532–535, 2000. ; and

[33568] Maekawa, M.; Ishizaki, T.; Boku, S.; Watanabe, N.; Fujita, A.; Iwamatsu, A.; Obinata, T.; Ohashi, K.; Mizuno, K.; Narumiya, S. : Signaling from Rho to the actin cytoskeleton through pro.

[33569] Further studies establishing the function and utilities of ARHC are found in John Hopkins OMIM database record ID 165380, and in cited publications numbered 10904–10905, 2155, 10909–1090 and 10910 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. BLTR2 (Accession NM\_019839) is another VGAM885 host target gene. BLTR2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by BLTR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of BLTR2 BINDING SITE, designated SEQ ID:21244, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33570] Another function of VGAM885 is therefore inhibition of BLTR2 (Accession NM\_019839). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BLTR2. Calpain 10 (CAPN10, Accession NM\_023084) is another VGAM885 host target gene. CAPN10 BINDING SITE1 through CAPN10 BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CAPN10, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAPN10 BINDING SITE1 through CAPN10 BINDING SITE4, designated SEQ ID:23347, SEQ ID:23349, SEQ ID:23351 and SEQ ID:23353 respectively, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33571] Another function of VGAM885 is therefore inhibition of Calpain 10 (CAPN10, Accession NM\_023084), a gene which catalyzes limited proteolysis of substrates involved in cytoskeletal remodelling and signal transduction. Ac-

cordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAPN10. The function of CAPN10 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM247. Cell Division Cycle 2-like 2 (CDC2L2, Accession NM\_033532) is another VGAM885 host target gene. CDC2L2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CDC2L2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDC2L2 BINDING SITE, designated SEQ ID:27301, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33572] Another function of VGAM885 is therefore inhibition of Cell Division Cycle 2-like 2 (CDC2L2, Accession NM\_033532). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDC2L2. Deoxyribonuclease I-like 1 (DNASE1L1, Accession NM\_006730) is another VGAM885 host target gene. DNASE1L1 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DNASE1L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNASE1L1 BINDING SITE, designated SEQ ID:13567, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33573] Another function of VGAM885 is therefore inhibition of Deoxyribonuclease I-like 1 (DNASE1L1, Accession NM\_006730), a gene which seems to be involved in cell death. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNASE1L1. The function of DNASE1L1 has been established by previous studies. Parrish et al. (1995) isolated a novel cDNA from the region of Xq28 between QM (OMIM Ref. No. 312173) and DXS1010E. Sequence similarity to DNase I (OMIM Ref. No. 125505) was high at the DNA and peptide sequence levels. The transcript was present at highest levels in skeletal and cardiac muscle, with lower expression in other tissues. Mutation analysis was performed using DNA samples from 2 unrelated patients with Barth syndrome (OMIM

Ref. No. 302060) and from 11 unrelated patients with Emery–Dreifuss muscular dystrophy (OMIM Ref. No. 310300), 2 genetic disorders involving muscle and with joint linkage to Xq28. No disease-associated mutations were detected in the coding region of the gene; however, Parrish et al. (1995) found a novel 190-bp insertion/deletion polymorphism in the 3-prime untranslated region. Translation of the long open reading frame found in the cDNA yielded a putative 302-amino acid protein with 37.6% identity to human DNase I. The protein was predicted to contain a signal sequence at the amino terminus, a transmembrane domain near the carboxyl terminus, and a helix–loop–helix domain. Pergolizzi et al. (1996) screened cDNA libraries with a cosmid that had been mapped to Xq28 in the region between RCP/GCP (303900; 303800) and G6PD (OMIM Ref. No. 305900). They obtained a 2.1-kb cDNA and showed that it encodes a putative 302-amino acid protein with 44% sequence identity to pig DNase I and 39% identity to human DNase I. Northern blots showed a single 2.0-kb transcript in adult heart and skeletal muscle and an additional transcript of 2.5 kb in some fetal tissues. (The sequence of Pergolizzi et al. (1996) was identical to that reported by Parrish et al.



(1995)).

[33574] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33575] Parrish, J. E.; Ciccodicola, A.; Wehnert, M.; Cox, G. F.; Chen, E.; Nelson, D. L. : A muscle-specific DNase I-like gene in human Xq28. Hum. Molec. Genet. 4: 1557–1564, 1995. ; and

[33576] Pergolizzi, R.; Appierto, V.; Bosetti, A.; DeBellis, G. L.; Rovida, E.; Biunno, I. : Cloning of a gene encoding a DNase I-like endonuclease in the human Xq28 region. Gene 168: 267–270.

[33577] Further studies establishing the function and utilities of DNASE1L1 are found in John Hopkins OMIM database record ID 300081, and in cited publications numbered 10970–10971 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Deoxyribonuclease II, Lysosomal (DNASE2, Accession NM\_001375) is another VGAM885 host target gene. DNASE2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DNASE2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of DNASE2 BINDING SITE, designated SEQ ID:7049, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33578] Another function of VGAM885 is therefore inhibition of Deoxyribonuclease II, Lysosomal (DNASE2, Accession NM\_001375), a gene which has a possible role in apoptosis. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNASE2. The function of DNASE2 has been established by previous studies. Yasuda et al. (1992) described a specific and highly sensitive assay for urinary and leukocytic DNASE2. In both urine and leukocytes, the enzyme showed clear-cut bimodality, and the Japanese study population could be classified into 2 distinct types, namely low-activity (DNASE2 L) and high-activity (DNASE2 H), which indicated the existence of a genetic polymorphism. Close correlations between the leukocytic and urinary enzyme activity levels from the same individuals were observed, and the types in the leukocyte samples agreed with the types found in the corresponding urine samples. In a group of 528 unrelated

Japanese individuals, the gene frequencies of the low-activity allele (DNASE2\*L) and the high-activity allele (DNASE2\*H) were calculated to be 0.632 and 0.368, respectively. Sex and age did not affect the distribution of the DNASE2 activity levels. Family studies indicated that the low-activity type is autosomal recessive. Using RACE with primers based on the sequence of purified DNase II protein to amplify thyroid RNA, Yasuda et al. (1998) cloned the DNase II gene. The predicted 360-amino acid protein has 3 parts: a 16-amino acid signal peptide, a 91-amino acid propeptide, and a 253-amino acid mature protein region. Yasuda et al. (1998) suggested that, like other lysosomal enzymes, DNase II is processed by release of a signal peptide followed by proteolytic processing that generates a 2-chain enzyme. Purified DNase II migrates as 2 bands (32 and 12 kD) on SDS-PAGE. Using RT-PCR, Yasuda et al. (1998) found that DNase II is expressed ubiquitously. Animal model experiments lend further support to the function of DNASE2. Mature erythrocytes in mammals have no nuclei, although they differentiate from nucleated precursor cells. Kawane et al. (2001) demonstrated that DNase II is indispensable for definitive erythropoiesis in mouse fetal liver. No live DNase II-null mice

were born, owing to severe anemia. When mutant fetal liver cells were transferred into lethally irradiated wildtype mice, mature red blood cells were generated from the mutant cells, suggesting that DNase II functions in a non-cell-autonomous manner. Histochemical analyses indicated that the critical cellular sources of DNase II are macrophages present at the site of definitive erythropoiesis in the fetal liver. Thus, Kawane et al. (2001) concluded that DNase II in macrophages appears to be responsible for destroying the nuclear DNA expelled from erythroid precursor cells.

[33579] It is appreciated that the abovementioned animal model for DNASE2 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[33580] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33581] Yasuda, T.; Nadano, D.; Sawazaki, K.; Kishi, K. : Genetic polymorphism of human deoxyribonuclease II (DNase II): low activity levels in urine and leukocytes are due to an autosomal recessive allele. *Ann. Hum. Genet.* 56: 1-10, 1992. ; and

[33582] Yasuda, T.; Takeshita, H.; Iida, R.; Nakajima, T.; Hosomi, O.; Nakashima, Y.; Kishi, K. : Molecular cloning of the cDNA encoding human deoxyribonuclease II. J. Biol. Chem. 273: 2610–261.

[33583] Further studies establishing the function and utilities of DNASE2 are found in John Hopkins OMIM database record ID 126350, and in cited publications numbered 3436–3441 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Hedgehog Interacting Protein (HHIP, Accession NM\_022475) is another VGAM885 host target gene. HHIP BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by HHIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HHIP BINDING SITE, designated SEQ ID:22842, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33584] Another function of VGAM885 is therefore inhibition of Hedgehog Interacting Protein (HHIP, Accession NM\_022475), a gene which is involved in many fundamental processes in embryonic development, including

anteroposterior patterns of limbs and regulation of left-right asymmetry. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HHIP. The function of HHIP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM329. Hermansky-Pudlak Syndrome 1 (HPS1, Accession NM\_000195) is another VGAM885 host target gene. HPS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HPS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HPS1 BINDING SITE, designated SEQ ID:5694, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33585] Another function of VGAM885 is therefore inhibition of Hermansky-Pudlak Syndrome 1 (HPS1, Accession NM\_000195). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HPS1. Interferon Gamma Receptor 2 (interferon gamma transducer 1) (IFNGR2, Ac-

cession NM\_005534) is another VGAM885 host target gene. IFNGR2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by IFNGR2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IFNGR2 BINDING SITE, designated SEQ ID:12054, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33586] Another function of VGAM885 is therefore inhibition of Interferon Gamma Receptor 2 (interferon gamma transducer 1) (IFNGR2, Accession NM\_005534), a gene which is required for signal transduction. this accessory factor is an integral part of the ifn-gamma signal transduction pathway and is likely to interact with gaf, jak1, and/or jak2. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IFNGR2. The function of IFNGR2 has been established by previous studies. For the cellular response of somatic cell hybrids (from fibroblasts) to gamma-interferon (OMIM Ref. No. 147570), the gamma-interferon receptor on 6q and a factor on chromosome

21q are necessary (Jung et al., 1987). Langer et al. (1990) demonstrated that the factor encoded by chromosome 21 is separate from the alpha and beta interferon receptors (see OMIM Ref. No. 107450) but maps to the same region. In hamster–human somatic cell hybrids, the presence of the IFN–gamma receptor–related factor mediating cellular responsiveness was determined by HLA induction in hybrid cells containing the IFN–gamma receptor on 6q, a transfected copy of the human HLA–B7 gene, and various portions of chromosome 21. In all hybrids, the IFNGT1 gene cosegregated with the IFNAR gene. (Presumably OMIM Ref. No. 107470.) Bono et al. (1991) likewise mapped this gene to chromosome 21 by study of somatic cell hybrids. Soh et al. (1993) identified a small region of chromosome 21 that is responsible for encoding accessory factor(s) by study of hamster–human somatic cell hybrids carrying an irradiation–reduced fragment of human chromosome 21. To localize the genes further, 10 different YAC clones from 6 different loci in the region were fused to a human–hamster hybrid cell line that contained 6q (supplying the interferon–gamma receptor) and the human HLA–B7 gene. These transformed cells were assayed for induction of class I HLA antigens upon treat–



ment with gamma-interferon. Soh et al. (1993) described a 540-kb YAC that could substitute for chromosome 21 in functioning as the accessory factor. The factor encoded by the YAC did not confer antiviral protection against the encephalomyocarditis virus, however, demonstrating that an additional factor encoded on human chromosome 21 is required for the antiviral activity. Mariano et al. (1996) mapped the *Ifgr2* gene to the distal end of mouse chromosome 16 by the study of interspecies backcrosses. Rhee et al. (1996) found that the *IFNGR2* gene spans over 33 kb of DNA and contains 7 exons. A signal peptide is encoded by exons 1 and 2, the extracellular domain by exons 2, 3, 4, 5, and part of 6. Exon 6 also encodes the entire transmembrane domain and part of the intracellular domain. Exon 7 encodes the remainder of the intracellular domain and contains the 3-prime untranslated region. No TATA or CAAT boxes were found in the promoter region. Consistent with the lack of a TATA box, analysis of mRNAs by primer extension showed multiple transcription start sites. Mutations in the IFN-gamma receptor ligand-binding chain (*IFNGR1*; 107470) have been shown to confer susceptibility to severe infection with nontuberculous mycobacteria. Dorman and Holland (1998) described a

mutation in the IFN- $\gamma$  receptor signal-transducing chain (OMIM Ref. No. IFNGR2) in a child with disseminated *Mycobacterium fortuitum* and *M. avium* complex infections, associated with absent IFN- $\gamma$  signaling due to a mutation in the extracellular domain of IFNGR2. The patient was a male who had 2 episodes of otitis media and 1 episode of thrush, all of which responded promptly to standard treatment. He received prescribed childhood immunizations but did not receive BCG vaccine. At 20 months of age, he developed a cough with pulmonary infiltrates that did not resolve with antibiotics. At 2 years of age, he developed lymphadenopathy, hepatosplenomegaly, and fevers. Biopsy of an axillary lymph node showed capsular fibrosis and histiocytic infiltration without abscesses or granulomata. Acid-fast bacilli were present on staining, and cultures grew the 2 forms of mycobacterium mentioned. Intensive therapy failed to eliminate the infection. The mother was of English descent and the father of English and Portuguese descent; they were not known to be related. A maternal aunt had been diagnosed with tuberculosis at age 3 years and subsequently developed cervical lymphadenopathy; she died at the age of 26 years of chronic aggressive hepatitis. In vitro cy-

tokine production by the patient's peripheral blood mononuclear cells showed 75% less PHA-induced interferon-gamma production than in normal cells, while the patient's PHA-induced TNF-alpha production was normal.

[33587] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33588] Rhee, S.; Ebensperger, C.; Dembic, Z.; Pestka, S. : The structure of the gene for the second chain of the human interferon-gamma receptor. J. Biol. Chem. 271: 28947-28952, 1996. ; and

[33589] Dorman, S. E.; Holland, S. M. : Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. J. Clin. Invest. 101: 2364-2369.

[33590] Further studies establishing the function and utilities of IFNGR2 are found in John Hopkins OMIM database record ID 147569, and in cited publications numbered 2733-2740 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Low Density Lipoprotein-related Protein 1 (alpha-2-macroglobulin receptor) (LRP1, Accession NM\_002332) is another VGAM885 host target gene. LRP1 BINDING SITE is HOST

TARGET binding site found in the 5' untranslated region of mRNA encoded by LRP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LRP1 BINDING SITE, designated SEQ ID:8137, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33591] Another function of VGAM885 is therefore inhibition of Low Density Lipoprotein-related Protein 1 (alpha-2-macroglobulin receptor) (LRP1, Accession NM\_002332), a gene which is a recycling lipoprotein receptor with possible growth-modulating effects. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LRP1. The function of LRP1 has been established by previous studies. Herz et al. (1988) cloned a cDNA for the low density lipoprotein receptor-related protein (LRP) by virtue of its close homology to the LDL receptor (OMIM Ref. No. 606945). Kristensen et al. (1990) and Strickland et al. (1990) demonstrated that LRP is identical to the alpha-2-macroglobulin (A2M; 103950) receptor (A2MR). Like the mannose-6-phosphate receptor (OMIM Ref. No.

147280), the A2MR/LRP molecule is probably bifunctional. The heat-shock protein gp96 (TRA1; 191175) is an intracellular protein capable of chaperoning exogenous antigens from tumors or virus-infected cells to antigen-presenting cells for presentation through major histocompatibility complex (MHC) class I rather than class II molecules, thereby eliciting CD8 (OMIM Ref. No. 186910)-positive T-cell responses. Using a mouse system, Binder et al. (2000) determined that the receptor for gp96 is CD91 (A2MR) and that A2M, a protein found in blood, inhibits gp96 binding to CD91. They proposed that CD91 acts as a sensor for necrotic cell death in tissues, leading to proinflammatory immune responses.

[33592] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33593] Strickland, D. K.; Ashcom, J. D.; Williams, S.; Burgess, W. H.; Migliorini, M.; Argraves, W. S. : Sequence identity between the alpha-2-macroglobulin receptor and low density lipoprotein receptor-related protein suggests that this molecule is a multifunctional receptor. J. Biol. Chem. 265: 17401-17404, 1990. ; and

[33594] Binder, R. J.; Han, D. K.; Srivastava, P. K. : CD91: a recep-

tor for heat shock protein gp96. Nature Immun. 1: 151–155, 2000.

[33595] Further studies establishing the function and utilities of LRP1 are found in John Hopkins OMIM database record ID 107770, and in cited publications numbered 12057–12061, 831, 12062–1206 and 12070–12068 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Nuclear Transcription Factor Y, Gamma (NFYC, Accession NM\_014223) is another VGAM885 host target gene. NFYC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NFYC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NFYC BINDING SITE, designated SEQ ID:15494, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33596] Another function of VGAM885 is therefore inhibition of Nuclear Transcription Factor Y, Gamma (NFYC, Accession NM\_014223). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NFYC. PACE (Accession

NM\_002569) is another VGAM885 host target gene. PACE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PACE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PACE BINDING SITE, designated SEQ ID:8427, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33597] Another function of VGAM885 is therefore inhibition of PACE (Accession NM\_002569), a gene which processes pro-parathyroid hormone, pro-transforming growth factor beta. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PACE. The function of PACE and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM151. Protein Kinase C and Casein Kinase Substrate In Neurons 1 (PACSIN1, Accession XM\_166424) is another VGAM885 host target gene. PACSIN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PACSIN1, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PACSIN1 BINDING SITE, designated SEQ ID:44316, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33598] Another function of VGAM885 is therefore inhibition of Protein Kinase C and Casein Kinase Substrate In Neurons 1 (PACSIN1, Accession XM\_166424). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PACSIN1. Paired Box Gene 8 (PAX8, Accession NM\_013953) is another VGAM885 host target gene. PAX8 BINDING SITE1 through PAX8 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by PAX8, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAX8 BINDING SITE1 through PAX8 BINDING SITE3, designated SEQ ID:15136, SEQ ID:15177 and SEQ ID:15135 respectively, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.



[33599] Another function of VGAM885 is therefore inhibition of Paired Box Gene 8 (PAX8, Accession NM\_013953), a gene which maintains the functional differentiation of thyroid cell type. Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAX8. The function of PAX8 has been established by previous studies. Pasca di Magliano et al. (2000) demonstrated that PAX8 is sufficient to activate expression of endogenous genes encoding thyroglobulin (TG; 188450), thyroperoxidase (TPO; 274500), and sodium/iodide symporter (SLC5A5; 601843), all thyroid-specific genes. The cell system they used provided direct evidence for the ability of PAX8 to activate transcription of thyroid-specific genes at their chromosomal locus and strongly suggested a fundamental role of this transcription factor in the maintenance of functional differentiation in thyroid cells. Moreover, they showed that PAX8 and thyroid transcription factor-1 (OMIM Ref. No. 600635) cooperate in the activation of the thyroglobulin promoter. Animal model experiments lend further support to the function of PAX8. The thyroid gland develops from 2 distinct embryonic lineages: follicular cells, which produce thyroxine and are of endodermal ori-

gin, and parafollicular C-cells, which produce calcitonin and are of neural crest origin. Mice lacking thyroid transcription factor-1 (OMIM Ref. No. 600635) lack both cell types and thus are unable to develop a thyroid gland. By analysis of Pax8 knockout mice (Pax8  $-/-$ ), Mansouri et al. (1998) demonstrated that Pax8 is required for the formation of the follicular cells in the thyroid. They presented evidence that Pax8 is necessary for providing cues for the differentiation of component endoderm primordia into thyroxine-producing follicular cells.

[33600] It is appreciated that the abovementioned animal model for PAX8 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[33601] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33602] Pasca di Magliano, M.; Di Lauro, R.; Zannini, M. : Pax8 has a key role in thyroid cell differentiation. Proc. Nat. Acad. Sci. 97: 13144–13149, 2000. ; and

[33603] Mansouri, A.; Chowdhury, K.; Gruss, P. : Follicular cells of the thyroid gland require Pax8 gene function. Nature Genet. 19: 87–90, 1998.

[33604] Further studies establishing the function and utilities of PAX8 are found in John Hopkins OMIM database record ID 167415, and in cited publications numbered 10774–10777, 10760, 10778, 10779, 10780, 1094 and 10947–10948 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RAD52 Homolog (*S. cerevisiae*) (RAD52, Accession NM\_134422) is another VGAM885 host target gene. RAD52 BINDING SITE1 through RAD52 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RAD52, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAD52 BINDING SITE1 through RAD52 BINDING SITE3, designated SEQ ID:28644, SEQ ID:28653 and SEQ ID:28662 respectively, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33605] Another function of VGAM885 is therefore inhibition of RAD52 Homolog (*S. cerevisiae*) (RAD52, Accession NM\_134422). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAD52. Baculoviral IAP Re-

peat-containing 8 (BIRC8, Accession NM\_033341) is another VGAM885 host target gene. BIRC8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BIRC8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BIRC8 BINDING SITE, designated SEQ ID:27196, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33606] Another function of VGAM885 is therefore inhibition of Baculoviral IAP Repeat-containing 8 (BIRC8, Accession NM\_033341). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BIRC8. Chromosome 5 Open Reading Frame 6 (C5orf6, Accession NM\_016605) is another VGAM885 host target gene. C5orf6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C5orf6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C5orf6 BINDING SITE, designated SEQ ID:18705, to the nucleotide se-

quence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33607] Another function of VGAM885 is therefore inhibition of Chromosome 5 Open Reading Frame 6 (C5orf6, Accession NM\_016605). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C5orf6. Cullin 2 (CUL2, Accession NM\_003591) is another VGAM885 host target gene. CUL2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CUL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CUL2 BINDING SITE, designated SEQ ID:9647, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33608] Another function of VGAM885 is therefore inhibition of Cullin 2 (CUL2, Accession NM\_003591). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CUL2. DKFZP434J037 (Accession NM\_030952) is another VGAM885 host target gene. DKFZP434J037 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by DKFZP434J037, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434J037 BINDING SITE, designated SEQ ID:25219, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33609] Another function of VGAM885 is therefore inhibition of DKFZP434J037 (Accession NM\_030952). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434J037. DKFZP564C1940 (Accession NM\_014045) is another VGAM885 host target gene. DKFZP564C1940 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZP564C1940, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564C1940 BINDING SITE, designated SEQ ID:15273, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33610] Another function of VGAM885 is therefore inhibition of

DKFZP564C1940 (Accession NM\_014045). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564C1940. DKFZp762A227 (Accession NM\_017611) is another VGAM885 host target gene. DKFZp762A227 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZp762A227, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp762A227 BINDING SITE, designated SEQ ID:19107, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33611] Another function of VGAM885 is therefore inhibition of DKFZp762A227 (Accession NM\_017611). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp762A227. EFS2 (Accession NM\_005864) is another VGAM885 host target gene. EFS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EFS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EFS2 BINDING SITE, designated SEQ ID:12478, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33612] Another function of VGAM885 is therefore inhibition of EFS2 (Accession NM\_005864). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EFS2. Four Jointed Box 1 (Drosophila) (FJX1, Accession NM\_014344) is another VGAM885 host target gene. FJX1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FJX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FJX1 BINDING SITE, designated SEQ ID:15663, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33613] Another function of VGAM885 is therefore inhibition of Four Jointed Box 1 (Drosophila) (FJX1, Accession NM\_014344). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clini-



cal conditions associated with FJX1. FLJ10898 (Accession XM\_002486) is another VGAM885 host target gene.

FLJ10898 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ10898, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10898 BINDING SITE, designated SEQ ID:29891, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33614] Another function of VGAM885 is therefore inhibition of FLJ10898 (Accession XM\_002486). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10898. FLJ21709 (Accession XM\_085480) is another VGAM885 host target gene. FLJ21709 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ21709, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21709 BINDING SITE, designated SEQ ID:38170, to the nucleotide sequence of

VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33615] Another function of VGAM885 is therefore inhibition of FLJ21709 (Accession XM\_085480). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21709. FLJ23476 (Accession NM\_024640) is another VGAM885 host target gene. FLJ23476 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23476, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23476 BINDING SITE, designated SEQ ID:23921, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33616] Another function of VGAM885 is therefore inhibition of FLJ23476 (Accession NM\_024640). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23476. Insulin-like Growth Factor 2, Antisense (IGF2AS, Accession NM\_016412) is another VGAM885 host target gene. IGF2AS BINDING SITE is HOST TARGET binding site found

in the 3' untranslated region of mRNA encoded by IGF2AS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IGF2AS BINDING SITE, designated SEQ ID:18540, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33617] Another function of VGAM885 is therefore inhibition of Insulin-like Growth Factor 2, Antisense (IGF2AS, Accession NM\_016412). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IGF2AS. Integrin, Beta 8 (ITGB8, Accession NM\_002214) is another VGAM885 host target gene. ITGB8 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ITGB8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGB8 BINDING SITE, designated SEQ ID:7978, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33618] Another function of VGAM885 is therefore inhibition of Integrin, Beta 8 (ITGB8, Accession NM\_002214). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ITGB8. KIAA0255 (Accession NM\_014742) is another VGAM885 host target gene. KIAA0255 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0255, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0255 BINDING SITE, designated SEQ ID:16416, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33619] Another function of VGAM885 is therefore inhibition of KIAA0255 (Accession NM\_014742). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0255. KIAA0275 (Accession NM\_014767) is another VGAM885 host target gene. KIAA0275 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0275, corresponding to a HOST TARGET binding site such as BINDING SITE I,

BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0275 BINDING SITE, designated SEQ ID:16553, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33620] Another function of VGAM885 is therefore inhibition of KIAA0275 (Accession NM\_014767). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0275. KIAA0514 (Accession NM\_014696) is another VGAM885 host target gene. KIAA0514 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0514, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0514 BINDING SITE, designated SEQ ID:16209, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33621] Another function of VGAM885 is therefore inhibition of KIAA0514 (Accession NM\_014696). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0514. KIAA0601 (Accession XM\_031267) is another VGAM885 host target gene. KIAA0601 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0601, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0601 BINDING SITE, designated SEQ ID:31327, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33622] Another function of VGAM885 is therefore inhibition of KIAA0601 (Accession XM\_031267). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0601. KIAA0769 (Accession NM\_014824) is another VGAM885 host target gene. KIAA0769 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0769, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0769 BINDING SITE, designated SEQ ID:16802, to the nucleotide sequence of VGAM885 RNA, herein designated

VGAM RNA, also designated SEQ ID:3596.

[33623] Another function of VGAM885 is therefore inhibition of KIAA0769 (Accession NM\_014824). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0769. KIAA0945 (Accession NM\_014952) is another VGAM885 host target gene. KIAA0945 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0945, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0945 BINDING SITE, designated SEQ ID:17296, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33624] Another function of VGAM885 is therefore inhibition of KIAA0945 (Accession NM\_014952). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0945. KIAA1161 (Accession XM\_088501) is another VGAM885 host target gene. KIAA1161 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1161, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1161 BINDING SITE, designated SEQ ID:39752, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33625] Another function of VGAM885 is therefore inhibition of KIAA1161 (Accession XM\_088501). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1161. KIAA1908 (Accession XM\_055834) is another VGAM885 host target gene. KIAA1908 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1908, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1908 BINDING SITE, designated SEQ ID:36335, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33626] Another function of VGAM885 is therefore inhibition of KIAA1908 (Accession XM\_055834). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with KIAA1908. Mitogen-activated Protein Kinase 8 Interacting Protein 3 (MAPK8IP3, Accession NM\_033392) is another VGAM885 host target gene. MAPK8IP3 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MAPK8IP3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAPK8IP3 BINDING SITE, designated SEQ ID:27220, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33627] Another function of VGAM885 is therefore inhibition of Mitogen-activated Protein Kinase 8 Interacting Protein 3 (MAPK8IP3, Accession NM\_033392). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAPK8IP3. MGC4172 (Accession NM\_024308) is another VGAM885 host target gene. MGC4172 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MGC4172, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of MGC4172 BINDING SITE, designated SEQ ID:23599, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33628] Another function of VGAM885 is therefore inhibition of MGC4172 (Accession NM\_024308). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4172. Purinergic Receptor P2X, Ligand-gated Ion Channel, 1 (P2RX1, Accession XM\_040635) is another VGAM885 host target gene. P2RX1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by P2RX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P2RX1 BINDING SITE, designated SEQ ID:33355, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33629] Another function of VGAM885 is therefore inhibition of Purinergic Receptor P2X, Ligand-gated Ion Channel, 1 (P2RX1, Accession XM\_040635). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with P2RX1. Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4B (SEMA4B, Accession XM\_044533) is another VGAM885 host target gene. SEMA4B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEMA4B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEMA4B BINDING SITE, designated SEQ ID:34225, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33630] Another function of VGAM885 is therefore inhibition of Sema Domain, Immunoglobulin Domain (Ig), Transmembrane Domain (TM) and Short Cytoplasmic Domain, (semaphorin) 4B (SEMA4B, Accession XM\_044533). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEMA4B. Sulfotransferase Family 4A, Member 1 (SULT4A1, Accession XM\_043609) is another VGAM885 host target gene. SULT4A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by SULT4A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SULT4A1 BINDING SITE, designated SEQ ID:33975, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33631] Another function of VGAM885 is therefore inhibition of Sulfotransferase Family 4A, Member 1 (SULT4A1, Accession XM\_043609). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SULT4A1. U5-116KD (Accession NM\_004247) is another VGAM885 host target gene. U5-116KD BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by U5-116KD, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of U5-116KD BINDING SITE, designated SEQ ID:10440, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33632] Another function of VGAM885 is therefore inhibition of

U5-116KD (Accession NM\_004247). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with U5-116KD. LOC115708 (Accession XM\_056552) is another VGAM885 host target gene. LOC115708 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC115708, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC115708 BINDING SITE, designated SEQ ID:36406, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33633] Another function of VGAM885 is therefore inhibition of LOC115708 (Accession XM\_056552). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC115708. LOC126432 (Accession XM\_059046) is another VGAM885 host target gene. LOC126432 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC126432, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC126432 BINDING SITE, designated SEQ ID:36840, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33634] Another function of VGAM885 is therefore inhibition of LOC126432 (Accession XM\_059046). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC126432. LOC129011 (Accession XM\_059326) is another VGAM885 host target gene. LOC129011 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC129011, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC129011 BINDING SITE, designated SEQ ID:36965, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33635] Another function of VGAM885 is therefore inhibition of LOC129011 (Accession XM\_059326). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129011. LOC145468 (Accession XM\_057874) is an-

other VGAM885 host target gene. LOC145468 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145468, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145468 BINDING SITE, designated SEQ ID:36549, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33636] Another function of VGAM885 is therefore inhibition of LOC145468 (Accession XM\_057874). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145468. LOC147072 (Accession XM\_017121) is another VGAM885 host target gene. LOC147072 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147072, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147072 BINDING SITE, designated SEQ ID:30298, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33637] Another function of VGAM885 is therefore inhibition of LOC147072 (Accession XM\_017121). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147072. LOC148304 (Accession XM\_086141) is another VGAM885 host target gene. LOC148304 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC148304, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148304 BINDING SITE, designated SEQ ID:38520, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33638] Another function of VGAM885 is therefore inhibition of LOC148304 (Accession XM\_086141). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148304. LOC148479 (Accession XM\_086204) is another VGAM885 host target gene. LOC148479 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC148479, corresponding to a HOST TARGET binding site such as BIND-



ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148479 BINDING SITE, designated SEQ ID:38540, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33639] Another function of VGAM885 is therefore inhibition of LOC148479 (Accession XM\_086204). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148479. LOC150155 (Accession XM\_047977) is another VGAM885 host target gene. LOC150155 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150155, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150155 BINDING SITE, designated SEQ ID:35091, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33640] Another function of VGAM885 is therefore inhibition of LOC150155 (Accession XM\_047977). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC150155. LOC151429 (Accession XM\_098059) is another VGAM885 host target gene. LOC151429 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151429, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151429 BINDING SITE, designated SEQ ID:41342, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33641] Another function of VGAM885 is therefore inhibition of LOC151429 (Accession XM\_098059). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151429. LOC152274 (Accession XM\_087418) is another VGAM885 host target gene. LOC152274 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152274, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152274 BINDING SITE, designated SEQ ID:39231, to the nucleotide sequence of VGAM885 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3596.

[33642] Another function of VGAM885 is therefore inhibition of LOC152274 (Accession XM\_087418). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152274. LOC152283 (Accession XM\_098196) is another VGAM885 host target gene. LOC152283 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152283, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152283 BINDING SITE, designated SEQ ID:41485, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33643] Another function of VGAM885 is therefore inhibition of LOC152283 (Accession XM\_098196). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152283. LOC158056 (Accession XM\_088463) is another VGAM885 host target gene. LOC158056 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158056, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158056 BINDING SITE, designated SEQ ID:39717, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33644] Another function of VGAM885 is therefore inhibition of LOC158056 (Accession XM\_088463). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158056. LOC161190 (Accession XM\_090747) is another VGAM885 host target gene. LOC161190 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC161190, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC161190 BINDING SITE, designated SEQ ID:40014, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33645] Another function of VGAM885 is therefore inhibition of LOC161190 (Accession XM\_090747). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161190. LOC200853 (Accession XM\_114308) is another VGAM885 host target gene. LOC200853 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC200853, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC200853 BINDING SITE, designated SEQ ID:42868, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33646] Another function of VGAM885 is therefore inhibition of LOC200853 (Accession XM\_114308). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC200853. LOC204965 (Accession XM\_117691) is another VGAM885 host target gene. LOC204965 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC204965, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC204965 BINDING SITE, designated SEQ ID:43575, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33647] Another function of VGAM885 is therefore inhibition of LOC204965 (Accession XM\_117691). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC204965. LOC219397 (Accession XM\_167889) is another VGAM885 host target gene. LOC219397 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219397 BINDING SITE, designated SEQ ID:44900, to the nucleotide sequence of VGAM885 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3596.

[33648] Another function of VGAM885 is therefore inhibition of LOC219397 (Accession XM\_167889). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219397. LOC219654 (Accession XM\_166095) is another VGAM885 host target gene. LOC219654 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219654, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219654 BINDING SITE, designated SEQ ID:43874, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33649] Another function of VGAM885 is therefore inhibition of LOC219654 (Accession XM\_166095). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219654. LOC219920 (Accession XM\_167787) is another VGAM885 host target gene. LOC219920 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC219920, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219920 BINDING SITE, designated SEQ ID:44808, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33650] Another function of VGAM885 is therefore inhibition of LOC219920 (Accession XM\_167787). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219920. LOC256239 (Accession XM\_170510) is another VGAM885 host target gene. LOC256239 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256239, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256239 BINDING SITE, designated SEQ ID:45344, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33651] Another function of VGAM885 is therefore inhibition of LOC256239 (Accession XM\_170510). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment



of diseases and clinical conditions associated with LOC256239. LOC91960 (Accession XM\_041872) is another VGAM885 host target gene. LOC91960 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91960, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91960 BINDING SITE, designated SEQ ID:33614, to the nucleotide sequence of VGAM885 RNA, herein designated VGAM RNA, also designated SEQ ID:3596.

[33652] Another function of VGAM885 is therefore inhibition of LOC91960 (Accession XM\_041872). Accordingly, utilities of VGAM885 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91960. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 886 (VGAM886) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33653] VGAM886 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM886 was detected is described hereinabove with reference to Figs. 1–8.

[33654] VGAM886 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM886 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33655] VGAM886 gene encodes a VGAM886 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM886 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM886 precursor RNA is designated SEQ ID:872, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:872 is located at position 68429 relative to the genome of Vaccinia Virus.

[33656] VGAM886 precursor RNA folds onto itself, forming VGAM886 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33657] An enzyme complex designated DICER COMPLEX, `dices` the VGAM886 folded precursor RNA into VGAM886 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM886 RNA is designated SEQ ID:3597, and is provided hereinbelow with reference to the sequence listing part.

[33658] VGAM886 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM886 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM886 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33659] VGAM886 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM886 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM886 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM886 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM886 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33660] The complementary binding of VGAM886 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM886 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM886 host target RNA into VGAM886 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33661] It is appreciated that VGAM886 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM886 host target genes. The mRNA of each one of this plurality of VGAM886 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM886 RNA, herein designated VGAM RNA, and which when bound by VGAM886 RNA causes inhibition of translation of respective one or more VGAM886 host target proteins.

[33662] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM886 gene, herein designated VGAM GENE, on one or more VGAM886 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other

known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33663] It is yet further appreciated that a function of VGAM886 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM886 correlate with, and may be deduced from, the identity of the host target genes which VGAM886 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33664] Nucleotide sequences of the VGAM886 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM886 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM886 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM886 are further described hereinbelow with reference to Table 1.

[33665] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM886 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM886 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33666] As mentioned hereinabove with reference to Fig. 1, a function of VGAM886 gene, herein designated VGAM is inhibition of expression of VGAM886 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM886 correlate with, and may be deduced from, the identity of the target genes which VGAM886 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33667] SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal) (SOX9, Accession NM\_000346) is a VGAM886 host target gene. SOX9 BIND-

ING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SOX9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOX9 BINDING SITE, designated SEQ ID:5899, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33668] A function of VGAM886 is therefore inhibition of SRY (sex determining region Y)-box 9 (campomelic dysplasia, autosomal sex-reversal) (SOX9, Accession NM\_000346), a gene which regulates the expression of other genes involved in chondrogenesis. Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOX9. The function of SOX9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM329.KIAA0982 (Accession NM\_014023) is another VGAM886 host target gene. KIAA0982 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0982, corresponding to a HOST TARGET binding site such as BINDING SITE I,



BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0982 BINDING SITE, designated SEQ ID:15247, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33669] Another function of VGAM886 is therefore inhibition of KIAA0982 (Accession NM\_014023). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0982. KIAA1028 (Accession XM\_166324) is another VGAM886 host target gene. KIAA1028 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1028, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1028 BINDING SITE, designated SEQ ID:44155, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33670] Another function of VGAM886 is therefore inhibition of KIAA1028 (Accession XM\_166324). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1028. PC2 (positive cofactor 2, multiprotein complex) Glutamine/Q-rich-associated Protein (PCQAP, Accession NM\_015889) is another VGAM886 host target gene. PC-QAP BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PCQAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCQAP BINDING SITE, designated SEQ ID:18032, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33671] Another function of VGAM886 is therefore inhibition of PC2 (positive cofactor 2, multiprotein complex) Glutamine/Q-rich-associated Protein (PCQAP, Accession NM\_015889). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCQAP. Protein Kinase, Lysine Deficient 2 (PRKWNK2, Accession XM\_117531) is another VGAM886 host target gene. PRKWNK2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PRKWNK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRKWNK2 BINDING SITE, designated SEQ ID:43523, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33672] Another function of VGAM886 is therefore inhibition of Protein Kinase, Lysine Deficient 2 (PRKWNK2, Accession XM\_117531). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRKWNK2. RCD-8 (Accession NM\_014329) is another VGAM886 host target gene. RCD-8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RCD-8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RCD-8 BINDING SITE, designated SEQ ID:15641, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33673] Another function of VGAM886 is therefore inhibition of RCD-8 (Accession NM\_014329). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with RCD-8. SMOC2 (Accession XM\_051452) is another VGAM886 host target gene. SMOC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SMOC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SMOC2 BINDING SITE, designated SEQ ID:35832, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33674] Another function of VGAM886 is therefore inhibition of SMOC2 (Accession XM\_051452). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SMOC2. Synaptojanin 2 (SYNJ2, Accession XM\_029746) is another VGAM886 host target gene. SYNJ2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SYNJ2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYNJ2 BINDING SITE, designated SEQ ID:30942, to the nucleotide sequence of

VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33675] Another function of VGAM886 is therefore inhibition of Synaptojanin 2 (SYNJ2, Accession XM\_029746). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYNJ2. Testis Specific, 14 (TSGA14, Accession NM\_018718) is another VGAM886 host target gene. TSGA14 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSGA14, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSGA14 BINDING SITE, designated SEQ ID:20793, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33676] Another function of VGAM886 is therefore inhibition of Testis Specific, 14 (TSGA14, Accession NM\_018718). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSGA14. LOC197201 (Accession XM\_113839) is another VGAM886 host target gene.

LOC197201 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197201, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197201 BINDING SITE, designated SEQ ID:42465, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33677] Another function of VGAM886 is therefore inhibition of LOC197201 (Accession XM\_113839). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197201. LOC219401 (Accession XM\_166706) is another VGAM886 host target gene. LOC219401 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC219401, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC219401 BINDING SITE, designated SEQ ID:44587, to the nucleotide sequence of VGAM886 RNA, herein designated VGAM RNA, also designated SEQ ID:3597.

[33678] Another function of VGAM886 is therefore inhibition of LOC219401 (Accession XM\_166706). Accordingly, utilities of VGAM886 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC219401. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 887 (VGAM887) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33679] VGAM887 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM887 was detected is described hereinabove with reference to Figs. 1–8.

[33680] VGAM887 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM887 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33681] VGAM887 gene encodes a VGAM887 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM887

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM887 precursor RNA is designated SEQ ID:873, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:873 is located at position 67126 relative to the genome of Vaccinia Virus.

[33682] VGAM887 precursor RNA folds onto itself, forming VGAM887 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33683] An enzyme complex designated DICER COMPLEX, `dices` the VGAM887 folded precursor RNA into VGAM887 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other



necessary proteins. A probable (over 42%) nucleotide sequence of VGAM887 RNA is designated SEQ ID:3598, and is provided hereinbelow with reference to the sequence listing part.

[33684] VGAM887 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM887 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM887 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33685] VGAM887 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM887 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM887 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM887 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM887 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33686] The complementary binding of VGAM887 RNA, herein designated VGAM RNA, to host target binding sites on VGAM887 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM887 host target RNA into VGAM887 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33687] It is appreciated that VGAM887 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM887 host target genes. The mRNA of each one of this plurality of VGAM887 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM887 RNA, herein designated VGAM RNA, and which when bound by VGAM887 RNA causes inhibition of translation of respective one or more VGAM887 host target proteins.

[33688] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM887 gene, herein designated VGAM GENE, on one or more VGAM887 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33689] It is yet further appreciated that a function of VGAM887 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM887 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM887 correlate with, and may be deduced from, the identity of the host target genes which VGAM887 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33690] Nucleotide sequences of the VGAM887 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM887 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM887 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM887 are further described hereinbelow with reference to Table 1.

[33691] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM887 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM887 RNA, herein designated VGAM RNA, are described hereinbelow with refer-

ence to Table 2.

[33692] As mentioned hereinabove with reference to Fig. 1, a function of VGAM887 gene, herein designated VGAM is inhibition of expression of VGAM887 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM887 correlate with, and may be deduced from, the identity of the target genes which VGAM887 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33693] Membrane Component, Chromosome 11, Surface Marker 1 (M11S1, Accession NM\_005898) is a VGAM887 host target gene. M11S1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by M11S1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of M11S1 BINDING SITE, designated SEQ ID:12516, to the nucleotide sequence of VGAM887 RNA, herein designated VGAM RNA, also designated SEQ ID:3598.

[33694] A function of VGAM887 is therefore inhibition of Membrane Component, Chromosome 11, Surface Marker 1 (M11S1, Accession NM\_005898), a gene which may play a

role in transporting nutrients from the gut lumen across the gutlining epithelial cell layer. Accordingly, utilities of VGAM887 include diagnosis, prevention and treatment of diseases and clinical conditions associated with M11S1. The function of M11S1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM131. Placenta-specific 1 (PLAC1, Accession NM\_021796) is another VGAM887 host target gene. PLAC1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by PLAC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PLAC1 BINDING SITE, designated SEQ ID:22352, to the nucleotide sequence of VGAM887 RNA, herein designated VGAM RNA, also designated SEQ ID:3598.

[33695] Another function of VGAM887 is therefore inhibition of Placenta-specific 1 (PLAC1, Accession NM\_021796). Accordingly, utilities of VGAM887 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PLAC1. Ubiquitin Protein Ligase E3A (human

papilloma virus E6-associated protein, Angelman syndrome) (UBE3A, Accession NM\_130838) is another VGAM887 host target gene. UBE3A BINDING SITE1 through UBE3A BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by UBE3A, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE3A BINDING SITE1 through UBE3A BINDING SITE3, designated SEQ ID:28360, SEQ ID:28364 and SEQ ID:6079 respectively, to the nucleotide sequence of VGAM887 RNA, herein designated VGAM RNA, also designated SEQ ID:3598.

[33696] Another function of VGAM887 is therefore inhibition of Ubiquitin Protein Ligase E3A (human papilloma virus E6-associated protein, Angelman syndrome) (UBE3A, Accession NM\_130838). Accordingly, utilities of VGAM887 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBE3A. LOC91250 (Accession XM\_037135) is another VGAM887 host target gene. LOC91250 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91250, corresponding to a HOST TARGET binding

site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91250 BINDING SITE, designated SEQ ID:32548, to the nucleotide sequence of VGAM887 RNA, herein designated VGAM RNA, also designated SEQ ID:3598.

[33697] Another function of VGAM887 is therefore inhibition of LOC91250 (Accession XM\_037135). Accordingly, utilities of VGAM887 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91250. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 888 (VGAM888) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33698] VGAM888 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM888 was detected is described hereinabove with reference to Figs. 1–8.

[33699] VGAM888 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 4.



VGAM888 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33700] VGAM888 gene encodes a VGAM888 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM888 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM888 precursor RNA is designated SEQ ID:874, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:874 is located at position 7588 relative to the genome of Human Herpesvirus 4.

[33701] VGAM888 precursor RNA folds onto itself, forming VGAM888 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33702] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM888 folded precursor RNA into VGAM888 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 91%) nucleotide sequence of VGAM888 RNA is designated SEQ ID:3599, and is provided hereinbelow with reference to the sequence listing part.

[33703] VGAM888 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM888 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM888 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33704] VGAM888 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM888 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM888 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM888 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM888 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33705] The complementary binding of VGAM888 RNA, herein designated VGAM RNA, to host target binding sites on VGAM888 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM888 host target RNA into VGAM888 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33706] It is appreciated that VGAM888 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM888 host target genes. The mRNA of each one of this plurality of VGAM888 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM888 RNA, herein designated VGAM RNA, and which when bound by VGAM888 RNA causes inhibition of translation of respective one or more VGAM888 host target proteins.

[33707] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM888 gene, herein designated VGAM GENE, on one or more VGAM888 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33708] It is yet further appreciated that a function of VGAM888 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM888 correlate with, and may be deduced from, the identity of the host target genes which VGAM888 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33709] Nucleotide sequences of the VGAM888 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM888 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM888 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM888 are further described hereinbelow with reference to Table 1.

- [33710] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM888 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM888 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33711] As mentioned hereinabove with reference to Fig. 1, a function of VGAM888 gene, herein designated VGAM is inhibition of expression of VGAM888 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM888 correlate with, and may be deduced from, the identity of the target genes which VGAM888 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [33712] Tumor Necrosis Factor (ligand) Superfamily, Member 4 (tax-transcriptionally activated glycoprotein 1, 34kDa) (TNFSF4, Accession NM\_003326) is a VGAM888 host target gene. TNFSF4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFSF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of TNFSF4 BINDING SITE, designated SEQ ID:9331, to the nucleotide sequence of VGAM888 RNA, herein designated VGAM RNA, also designated SEQ ID:3599.

[33713] A function of VGAM888 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 4 (tax-transcriptionally activated glycoprotein 1, 34kDa) (TNFSF4, Accession NM\_003326), a gene which co-stimulates t cell proliferation and cytokine production. Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFSF4. The function of TNFSF4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM463.FLJ20038 (Accession NM\_017634) is another VGAM888 host target gene. FLJ20038 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20038 BINDING SITE, designated SEQ ID:19141, to the nucleotide sequence of VGAM888

RNA, herein designated VGAM RNA, also designated SEQ ID:3599.

[33714] Another function of VGAM888 is therefore inhibition of FLJ20038 (Accession NM\_017634). Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20038. KIAA1805 (Accession XM\_086976) is another VGAM888 host target gene. KIAA1805 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1805, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1805 BINDING SITE, designated SEQ ID:39000, to the nucleotide sequence of VGAM888 RNA, herein designated VGAM RNA, also designated SEQ ID:3599.

[33715] Another function of VGAM888 is therefore inhibition of KIAA1805 (Accession XM\_086976). Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1805. MSTP032 (Accession NM\_025226) is another VGAM888 host target gene. MSTP032 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by MSTP032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSTP032 BINDING SITE, designated SEQ ID:24908, to the nucleotide sequence of VGAM888 RNA, herein designated VGAM RNA, also designated SEQ ID:3599.

[33716] Another function of VGAM888 is therefore inhibition of MSTP032 (Accession NM\_025226). Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSTP032. NCK Adaptor Protein 1 (NCK1, Accession NM\_006153) is another VGAM888 host target gene. NCK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCK1 BINDING SITE, designated SEQ ID:12810, to the nucleotide sequence of VGAM888 RNA, herein designated VGAM RNA, also designated SEQ ID:3599.

[33717] Another function of VGAM888 is therefore inhibition of NCK Adaptor Protein 1 (NCK1, Accession NM\_006153).

Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCK1. LOC120114 (Accession XM\_061871) is another VGAM888 host target gene. LOC120114 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120114 BINDING SITE, designated SEQ ID:37214, to the nucleotide sequence of VGAM888 RNA, herein designated VGAM RNA, also designated SEQ ID:3599.

[33718] Another function of VGAM888 is therefore inhibition of LOC120114 (Accession XM\_061871). Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120114. LOC146669 (Accession XM\_085534) is another VGAM888 host target gene. LOC146669 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146669, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC146669 BINDING SITE, designated SEQ ID:38223, to the nucleotide sequence of VGAM888 RNA, herein designated VGAM RNA, also designated SEQ ID:3599.

[33719] Another function of VGAM888 is therefore inhibition of LOC146669 (Accession XM\_085534). Accordingly, utilities of VGAM888 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146669. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 889 (VGAM889) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33720] VGAM889 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM889 was detected is described hereinabove with reference to Figs. 1–8.

[33721] VGAM889 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 4. VGAM889 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[33722] VGAM889 gene encodes a VGAM889 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM889 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM889 precursor RNA is designated SEQ ID:875, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:875 is located at position 9562 relative to the genome of Human Herpesvirus 4.

[33723] VGAM889 precursor RNA folds onto itself, forming VGAM889 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33724] An enzyme complex designated DICER COMPLEX, `dices` the VGAM889 folded precursor RNA into VGAM889 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM889 RNA is designated SEQ ID:3600, and is provided hereinbelow with reference to the sequence listing part.

[33725] VGAM889 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM889 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM889 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33726] VGAM889 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM889 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM889 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-

quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM889 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM889 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33727] The complementary binding of VGAM889 RNA, herein designated VGAM RNA, to host target binding sites on VGAM889 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM889 host target RNA into VGAM889 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33728] It is appreciated that VGAM889 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM889 host target genes. The mRNA of each one of this plurality of VGAM889 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM889 RNA, herein designated VGAM RNA, and which when bound by VGAM889 RNA causes inhibition of translation of respective one or more VGAM889 host target proteins.

[33729] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM889 gene, herein designated VGAM GENE, on one or more VGAM889 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33730] It is yet further appreciated that a function of VGAM889 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM889 correlate with, and may be deduced from, the identity of the host target genes which VGAM889 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33731] Nucleotide sequences of the VGAM889 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM889 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM889 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM889 are further described hereinbelow with reference to Table 1.

[33732] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of



Fig. 1, found on VGAM889 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM889 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33733] As mentioned hereinabove with reference to Fig. 1, a function of VGAM889 gene, herein designated VGAM is inhibition of expression of VGAM889 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM889 correlate with, and may be deduced from, the identity of the target genes which VGAM889 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33734] Microfibrillar-associated Protein 4 (MFAP4, Accession XM\_045044) is a VGAM889 host target gene. MFAP4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MFAP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MFAP4 BINDING SITE, designated SEQ ID:34328, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33735] A function of VGAM889 is therefore inhibition of Microfibrillar-associated Protein 4 (MFAP4, Accession XM\_045044). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MFAP4. Transient Receptor Potential Cation Channel, Subfamily M, Member 6 (TRPM6, Accession NM\_017662) is another VGAM889 host target gene. TRPM6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRPM6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRPM6 BINDING SITE, designated SEQ ID:19197, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33736] Another function of VGAM889 is therefore inhibition of Transient Receptor Potential Cation Channel, Subfamily M, Member 6 (TRPM6, Accession NM\_017662), a gene which contains a predicted ion channel domain and a protein kinase domain. Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRPM6. The function of

TRPM6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM173. Chromosome 20 Open Reading Frame 30 (C20orf30, Accession NM\_014145) is another VGAM889 host target gene. C20orf30 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf30, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf30 BINDING SITE, designated SEQ ID:15431, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33737] Another function of VGAM889 is therefore inhibition of Chromosome 20 Open Reading Frame 30 (C20orf30, Accession NM\_014145). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf30. DKFZP434P211 (Accession NM\_014549) is another VGAM889 host target gene. DKFZP434P211 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by DKFZP434P211, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434P211 BINDING SITE, designated SEQ ID:15866, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33738] Another function of VGAM889 is therefore inhibition of DKFZP434P211 (Accession NM\_014549). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434P211. Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A (GRIN3A, Accession NM\_133445) is another VGAM889 host target gene. GRIN3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRIN3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRIN3A BINDING SITE, designated SEQ ID:28531, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33739] Another function of VGAM889 is therefore inhibition of Glutamate Receptor, Ionotropic, N-methyl-D-aspartate 3A

(GRIN3A, Accession NM\_133445). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRIN3A. IMP-2 (Accession NM\_006548) is another VGAM889 host target gene. IMP-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IMP-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IMP-2 BINDING SITE, designated SEQ ID:13303, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33740] Another function of VGAM889 is therefore inhibition of IMP-2 (Accession NM\_006548). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IMP-2. KIAA0164 (Accession NM\_014739) is another VGAM889 host target gene. KIAA0164 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0164, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of KIAA0164 BINDING SITE, designated SEQ ID:16405, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33741] Another function of VGAM889 is therefore inhibition of KIAA0164 (Accession NM\_014739). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0164. KIAA1389 (Accession XM\_045839) is another VGAM889 host target gene. KIAA1389 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1389, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1389 BINDING SITE, designated SEQ ID:34569, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33742] Another function of VGAM889 is therefore inhibition of KIAA1389 (Accession XM\_045839). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1389. KIAA1416 (Accession XM\_098762) is another

VGAM889 host target gene. KIAA1416 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1416, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1416 BINDING SITE, designated SEQ ID:41801, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33743] Another function of VGAM889 is therefore inhibition of KIAA1416 (Accession XM\_098762). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1416. T-cell Leukemia/lymphoma 6 (TCL6, Accession NM\_020552) is another VGAM889 host target gene. TCL6 BINDING SITE1 and TCL6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TCL6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TCL6 BINDING SITE1 and TCL6 BINDING SITE2, designated SEQ ID:21769 and SEQ ID:21775 respectively, to the nucleotide sequence of

VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33744] Another function of VGAM889 is therefore inhibition of T-cell Leukemia/lymphoma 6 (TCL6, Accession NM\_020552). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TCL6. LOC199858 (Accession XM\_114040) is another VGAM889 host target gene. LOC199858 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC199858, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199858 BINDING SITE, designated SEQ ID:42633, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33745] Another function of VGAM889 is therefore inhibition of LOC199858 (Accession XM\_114040). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199858. LOC256176 (Accession XM\_172889) is another VGAM889 host target gene. LOC256176 BINDING



SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC256176, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256176 BINDING SITE, designated SEQ ID:46170, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33746] Another function of VGAM889 is therefore inhibition of LOC256176 (Accession XM\_172889). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256176. LOC57105 (Accession NM\_020377) is another VGAM889 host target gene. LOC57105 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC57105, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57105 BINDING SITE, designated SEQ ID:21637, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33747] Another function of VGAM889 is therefore inhibition of

LOC57105 (Accession NM\_020377). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57105. LOC81558 (Accession NM\_030802) is another VGAM889 host target gene. LOC81558 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC81558, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC81558 BINDING SITE, designated SEQ ID:25109, to the nucleotide sequence of VGAM889 RNA, herein designated VGAM RNA, also designated SEQ ID:3600.

[33748] Another function of VGAM889 is therefore inhibition of LOC81558 (Accession NM\_030802). Accordingly, utilities of VGAM889 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC81558. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 890 (VGAM890) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[33749] VGAM890 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM890 was detected is described hereinabove with reference to Figs. 1–8.

[33750] VGAM890 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 4. VGAM890 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33751] VGAM890 gene encodes a VGAM890 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM890 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM890 precursor RNA is designated SEQ ID:876, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:876 is located at position 8059 relative to the genome of Human Herpesvirus 4.

[33752] VGAM890 precursor RNA folds onto itself, forming VGAM890 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[33753] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM890 folded precursor RNA into VGAM890 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 40%) nucleotide se-  
quence of VGAM890 RNA is designated SEQ ID:3601, and  
is provided hereinbelow with reference to the sequence  
listing part.

[33754] VGAM890 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM890 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM890 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[33755] VGAM890 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM890 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM890 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM890 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM890 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[33756] The complementary binding of VGAM890 RNA, herein designated VGAM RNA, to host target binding sites on VGAM890 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM890 host target RNA into VGAM890 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33757] It is appreciated that VGAM890 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM890 host target genes. The mRNA of each one of this plurality of VGAM890 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM890 RNA, herein designated VGAM RNA, and which when bound by VGAM890 RNA causes inhibition of translation of respective one or more VGAM890 host target proteins.

[33758] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM890 gene, herein designated VGAM GENE, on one or

more VGAM890 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33759] It is yet further appreciated that a function of VGAM890 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM890 correlate with, and may be deduced from, the identity of the host target genes which VGAM890 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [33760] Nucleotide sequences of the VGAM890 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM890 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM890 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM890 are further described hereinbelow with reference to Table 1.
- [33761] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM890 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM890 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [33762] As mentioned hereinabove with reference to Fig. 1, a function of VGAM890 gene, herein designated VGAM is inhibition of expression of VGAM890 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM890 correlate with, and may be deduced from, the identity of the target genes which VGAM890 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [33763] GAC1 (Accession NM\_006338) is a VGAM890 host target



gene. GAC1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GAC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAC1 BINDING SITE, designated SEQ ID:13036, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33764] A function of VGAM890 is therefore inhibition of GAC1 (Accession NM\_006338). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAC1. Leucine Zipper, Putative Tumor Suppressor 1 (LZTS1, Accession NM\_021020) is another VGAM890 host target gene. LZTS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LZTS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LZTS1 BINDING SITE, designated SEQ ID:22004, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33765] Another function of VGAM890 is therefore inhibition of Leucine Zipper, Putative Tumor Suppressor 1 (LZTS1, Accession NM\_021020), a gene which Zygin 1; may have a role in axonal outgrowth; has similarity to *C. elegans* UNC-76. Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LZTS1. The function of LZTS1 has been established by previous studies. Ishii et al. (1999) positionally cloned and characterized the FEZ1/LZTS1 (leucine zipper, putative tumor suppressor-1) gene at 8p22, a region that is lost in many tumors, including prostate, breast, head and neck, esophageal, and urinary bladder carcinomas. The predicted FEZ1 protein contained a leucine-zipper region with similarity to the DNA-binding domain of the cAMP-responsive activating transcription factor-5 (OMIM Ref. No. 606398). Northern blot analysis revealed that FEZ2 is expressed almost ubiquitously in normal tissues, although expression is most abundant in testes. FEZ1 expression was undetectable in more than 60% of epithelial tumors, but FEZ1 mutations were found in primary esophageal cancers and in a prostate cancer cell line. Transcript analysis from several FEZ1-expressing tumors revealed truncated mRNAs, in-

cluding a frameshift. Alteration and inactivation of the FEZ1 gene may play a role in various human tumors. Ishii et al. (2001) showed that introduction of FEZ1/LZTS1 into FEZ1/LZTS1-negative cancer cells resulted in suppression of tumorigenicity and reduced cell growth with accumulation of cells at late S-G2/M stage of the cell cycle. Their data showed that FEZ1/LZTS1 inhibits cancer cell growth through regulation of mitosis, and that its alterations result in abnormal cell growth. Ishii et al. (1999) analyzed the nucleotide sequence of the FEZ1 gene open reading frame in 194 cancers, including 72 primary esophageal cancers. They found a point mutation in 2 primary esophageal cancers and in a prostate cancer cell line.

[33766] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33767] Ishii, H.; Baffa, R.; Numata, S.-I.; Murakumo, Y.; Rattan, S.; Inoue, H.; Mori, M.; Fidanza, V.; Alder, H.; Croce, C. M. : The FEZ1 gene at chromosome 8p22 encodes a leucine-zipper protein, and its expression is altered in multiple human tumors. Proc. Nat. Acad. Sci. 96: 3928-3933, 1999. ; and

[33768] Ishii, H.; Vecchione, A.; Murakumo, Y.; Baldassarre, G.;

Numata, S.; Trapasso, F.; Alder, H.; Baffa, R.; Croce, C. M. :  
FEZ1/LZTS1 gene at 8p22 suppresses cancer cell growth  
and regula.

[33769] Further studies establishing the function and utilities of  
LZTS1 are found in John Hopkins OMIM database record ID  
606551, and in cited publications numbered 4650 listed  
in the bibliography section hereinbelow, which are also  
hereby incorporated by reference. Sulfite Oxidase (SUOX,  
Accession NM\_000456) is another VGAM890 host target  
gene. SUOX BINDING SITE is HOST TARGET binding site  
found in the 5' untranslated region of mRNA encoded by  
SUOX, corresponding to a HOST TARGET binding site such  
as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-  
ble 2 illustrates the complementarity of the nucleotide se-  
quences of SUOX BINDING SITE, designated SEQ ID:6071,  
to the nucleotide sequence of VGAM890 RNA, herein des-  
ignated VGAM RNA, also designated SEQ ID:3601.

[33770] Another function of VGAM890 is therefore inhibition of  
Sulfite Oxidase (SUOX, Accession NM\_000456), a gene  
which sulfite oxidase deficiency. Accordingly, utilities of  
VGAM890 include diagnosis, prevention and treatment of  
diseases and clinical conditions associated with SUOX. The  
function of SUOX has been established by previous stud-

ies. Garrett et al. (1995) isolated a 2.4-kb cDNA clone of human sulfite oxidase from a human liver cDNA library. The deduced 488-amino acid protein has a molecular mass of approximately 52 kD and shows 88% homology to the rat protein and 67% homology to the chicken protein. Comparison of 3 sulfite oxidase sequences to several plant and fungal nitrate reductase sequences revealed a single conserved cysteine with highly conserved flanking sequences. Garrett et al. (1995) postulated that the conserved cysteine is a ligand of molybdenum in sulfite oxidase and nitrate reductase. Kisker et al. (1997) determined the crystal structure of chicken liver sulfite oxidase, which is homologous to the human protein, at 1.9-angstrom resolution. They found that each monomer of the dimeric enzyme consists of 3 domains. At the active site, the Mo is penta-coordinated by 3 sulfur ligands, 1 oxo group, and 1 water/hydroxo. A sulfate molecule adjacent to the Mo identifies the substrate binding pocket.

[33771] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33772] Garrett, R. M.; Bellissimo, D. B.; Rajagopalan, K. V. : Molecular cloning of human liver sulfite oxidase. *Biochim.*

Biophys. Acta 1262: 147–149, 1995. ; and

[33773] Kisker, C.; Schindelin, H.; Pacheco, A.; Wehbi, W. A.; Garrett, R. M.; Rajagopalan, K. V.; Enemark, J. H.; Rees, D. C. : Molecular basis of sulfite oxidase deficiency from the structur.

[33774] Further studies establishing the function and utilities of SUOX are found in John Hopkins OMIM database record ID 606887, and in cited publications numbered 5393, 870 and 8706 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.FLJ20297 (Accession NM\_017751) is another VGAM890 host target gene. FLJ20297 BINDING SITE1 and FLJ20297 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FLJ20297, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20297 BINDING SITE1 and FLJ20297 BINDING SITE2, designated SEQ ID:19357 and SEQ ID:19646 respectively, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33775] Another function of VGAM890 is therefore inhibition of FLJ20297 (Accession NM\_017751). Accordingly, utilities of

VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20297. KIAA1867 (Accession XM\_170675) is another VGAM890 host target gene. KIAA1867 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1867, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1867 BINDING SITE, designated SEQ ID:45453, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33776] Another function of VGAM890 is therefore inhibition of KIAA1867 (Accession XM\_170675). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1867. KIAA1940 (Accession XM\_086981) is another VGAM890 host target gene. KIAA1940 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1940, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA1940 BINDING SITE, designated SEQ ID:39009, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33777] Another function of VGAM890 is therefore inhibition of KIAA1940 (Accession XM\_086981). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1940. Peptidylprolyl Isomerase (cyclophilin)-like 2 (PPIL2, Accession NM\_014337) is another VGAM890 host target gene. PPIL2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PPIL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPIL2 BINDING SITE, designated SEQ ID:15649, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33778] Another function of VGAM890 is therefore inhibition of Peptidylprolyl Isomerase (cyclophilin)-like 2 (PPIL2, Accession NM\_014337). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPIL2. PR Domain Con-



taining 10 (PRDM10, Accession NM\_020228) is another VGAM890 host target gene. PRDM10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRDM10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRDM10 BINDING SITE, designated SEQ ID:21496, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33779] Another function of VGAM890 is therefore inhibition of PR Domain Containing 10 (PRDM10, Accession NM\_020228). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRDM10. TOPBP1 (Accession NM\_007027) is another VGAM890 host target gene. TOPBP1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TOPBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOPBP1 BINDING SITE, designated SEQ ID:13886, to the nucleotide sequence of VGAM890 RNA, herein designated

VGAM RNA, also designated SEQ ID:3601.

[33780] Another function of VGAM890 is therefore inhibition of TOPBP1 (Accession NM\_007027). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOPBP1. LOC150776 (Accession XM\_032542) is another VGAM890 host target gene. LOC150776 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC150776, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150776 BINDING SITE, designated SEQ ID:31673, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33781] Another function of VGAM890 is therefore inhibition of LOC150776 (Accession XM\_032542). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150776. LOC152274 (Accession XM\_087418) is another VGAM890 host target gene. LOC152274 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152274, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152274 BINDING SITE, designated SEQ ID:39230, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33782] Another function of VGAM890 is therefore inhibition of LOC152274 (Accession XM\_087418). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152274. LOC199837 (Accession XM\_114034) is another VGAM890 host target gene. LOC199837 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC199837, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199837 BINDING SITE, designated SEQ ID:42626, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33783] Another function of VGAM890 is therefore inhibition of LOC199837 (Accession XM\_114034). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC199837. LOC255104 (Accession XM\_170911) is another VGAM890 host target gene. LOC255104 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC255104, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255104 BINDING SITE, designated SEQ ID:45682, to the nucleotide sequence of VGAM890 RNA, herein designated VGAM RNA, also designated SEQ ID:3601.

[33784] Another function of VGAM890 is therefore inhibition of LOC255104 (Accession XM\_170911). Accordingly, utilities of VGAM890 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255104. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 891 (VGAM891) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33785] VGAM891 is a novel bioinformatically detected regulatory,

non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM891 was detected is described hereinabove with reference to Figs. 1–8.

[33786] VGAM891 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 4. VGAM891 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33787] VGAM891 gene encodes a VGAM891 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM891 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM891 precursor RNA is designated SEQ ID:877, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:877 is located at position 7900 relative to the genome of Human Herpesvirus 4.

[33788] VGAM891 precursor RNA folds onto itself, forming VGAM891 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA

genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33789] An enzyme complex designated DICER COMPLEX, `dices` the VGAM891 folded precursor RNA into VGAM891 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 91%) nucleotide sequence of VGAM891 RNA is designated SEQ ID:3602, and is provided hereinbelow with reference to the sequence listing part.

[33790] VGAM891 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM891 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM891 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33791] VGAM891 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM891 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM891 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM891 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM891 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33792] The complementary binding of VGAM891 RNA, herein

designated VGAM RNA, to host target binding sites on VGAM891 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM891 host target RNA into VGAM891 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33793] It is appreciated that VGAM891 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM891 host target genes. The mRNA of each one of this plurality of VGAM891 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM891 RNA, herein designated VGAM RNA, and which when bound by VGAM891 RNA causes inhibition of translation of respective one or more VGAM891 host target proteins.

[33794] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM891 gene, herein designated VGAM GENE, on one or more VGAM891 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other



known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33795] It is yet further appreciated that a function of VGAM891 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM891 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 4. Specific functions, and accordingly utilities, of VGAM891 correlate with, and may be deduced from, the identity of the host target genes which VGAM891 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33796] Nucleotide sequences of the VGAM891 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the

`diced` VGAM891 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM891 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM891 are further described hereinbelow with reference to Table 1.

[33797] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM891 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM891 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33798] As mentioned hereinabove with reference to Fig. 1, a function of VGAM891 gene, herein designated VGAM is inhibition of expression of VGAM891 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM891 correlate with, and may be deduced from, the identity of the target genes which VGAM891 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33799] Tumor Necrosis Factor (ligand) Superfamily, Member 4 (tax-transcriptionally activated glycoprotein 1, 34kDa) (TNFSF4, Accession NM\_003326) is a VGAM891 host tar-

get gene. TNFSF4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TNFSF4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFSF4 BINDING SITE, designated SEQ ID:9331, to the nucleotide sequence of VGAM891 RNA, herein designated VGAM RNA, also designated SEQ ID:3602.

[33800] A function of VGAM891 is therefore inhibition of Tumor Necrosis Factor (ligand) Superfamily, Member 4 (tax-transcriptionally activated glycoprotein 1, 34kDa) (TNFSF4, Accession NM\_003326), a gene which co-stimulates t cell proliferation and cytokine production. Accordingly, utilities of VGAM891 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFSF4. The function of TNFSF4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM463.FLJ20038 (Accession NM\_017634) is another VGAM891 host target gene. FLJ20038 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded

by FLJ20038, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20038 BINDING SITE, designated SEQ ID:19141, to the nucleotide sequence of VGAM891 RNA, herein designated VGAM RNA, also designated SEQ ID:3602.

[33801] Another function of VGAM891 is therefore inhibition of FLJ20038 (Accession NM\_017634). Accordingly, utilities of VGAM891 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20038. KIAA1805 (Accession XM\_086976) is another VGAM891 host target gene. KIAA1805 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1805, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1805 BINDING SITE, designated SEQ ID:39000, to the nucleotide sequence of VGAM891 RNA, herein designated VGAM RNA, also designated SEQ ID:3602.

[33802] Another function of VGAM891 is therefore inhibition of KIAA1805 (Accession XM\_086976). Accordingly, utilities

of VGAM891 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1805. MSTP032 (Accession NM\_025226) is another VGAM891 host target gene. MSTP032 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSTP032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSTP032 BINDING SITE, designated SEQ ID:24908, to the nucleotide sequence of VGAM891 RNA, herein designated VGAM RNA, also designated SEQ ID:3602.

[33803] Another function of VGAM891 is therefore inhibition of MSTP032 (Accession NM\_025226). Accordingly, utilities of VGAM891 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSTP032. NCK Adaptor Protein 1 (NCK1, Accession NM\_006153) is another VGAM891 host target gene. NCK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCK1 BIND-

ING SITE, designated SEQ ID:12810, to the nucleotide sequence of VGAM891 RNA, herein designated VGAM RNA, also designated SEQ ID:3602.

[33804] Another function of VGAM891 is therefore inhibition of NCK Adaptor Protein 1 (NCK1, Accession NM\_006153). Accordingly, utilities of VGAM891 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCK1. LOC120114 (Accession XM\_061871) is another VGAM891 host target gene. LOC120114 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120114 BINDING SITE, designated SEQ ID:37214, to the nucleotide sequence of VGAM891 RNA, herein designated VGAM RNA, also designated SEQ ID:3602.

[33805] Another function of VGAM891 is therefore inhibition of LOC120114 (Accession XM\_061871). Accordingly, utilities of VGAM891 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120114. LOC146669 (Accession XM\_085534) is an-

other VGAM891 host target gene. LOC146669 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146669, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146669 BINDING SITE, designated SEQ ID:38223, to the nucleotide sequence of VGAM891 RNA, herein designated VGAM RNA, also designated SEQ ID:3602.

[33806] Another function of VGAM891 is therefore inhibition of LOC146669 (Accession XM\_085534). Accordingly, utilities of VGAM891 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146669. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 892 (VGAM892) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33807] VGAM892 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM892 was detected is described

hereinabove with reference to Figs. 1–8.

[33808] VGAM892 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Periplaneta Fuliginosa Densovirus. VGAM892 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33809] VGAM892 gene encodes a VGAM892 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM892 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM892 precursor RNA is designated SEQ ID:878, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:878 is located at position 4066 relative to the genome of Periplaneta Fuliginosa Densovirus.

[33810] VGAM892 precursor RNA folds onto itself, forming VGAM892 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an



accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33811] An enzyme complex designated DICER COMPLEX, `dices` the VGAM892 folded precursor RNA into VGAM892 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM892 RNA is designated SEQ ID:3603, and is provided hereinbelow with reference to the sequence listing part.

[33812] VGAM892 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM892 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM892 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33813] VGAM892 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM892 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM892 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM892 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM892 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33814] The complementary binding of VGAM892 RNA, herein designated VGAM RNA, to host target binding sites on VGAM892 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM892 host target RNA into VGAM892 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33815] It is appreciated that VGAM892 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM892 host target genes. The mRNA of each one of this plurality of VGAM892 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM892 RNA, herein designated VGAM RNA, and which when bound by VGAM892 RNA causes inhibition of translation of respective one or more VGAM892 host target proteins.

[33816] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM892 gene, herein designated VGAM GENE, on one or more VGAM892 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33817] It is yet further appreciated that a function of VGAM892 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM892 include diagnosis, prevention and treatment of viral infection by Periplaneta Fuliginosa Densovirus. Specific functions, and accordingly utilities, of VGAM892 correlate with, and may be deduced from, the identity of the host target genes which VGAM892 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33818] Nucleotide sequences of the VGAM892 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM892 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM892 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM892 are further described hereinbelow with reference to Table 1.

[33819] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM892 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM892 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33820] As mentioned hereinabove with reference to Fig. 1, a function of VGAM892 gene, herein designated VGAM is inhibition of expression of VGAM892 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM892 correlate with, and may be deduced from, the identity of the target genes which VGAM892 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33821] Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Accession NM\_003842) is a VGAM892 host target gene. TNFRSF10B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TNFRSF10B, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFRSF10B BINDING SITE, designated SEQ ID:9939, to the nucleotide sequence of VGAM892 RNA, herein designated VGAM RNA, also designated SEQ ID:3603.

[33822] A function of VGAM892 is therefore inhibition of Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Accession NM\_003842), a gene which forms complex that induces apoptosis. Accordingly, utilities of VGAM892 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFRSF10B. The function of TNFRSF10B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM400. LOC146880 (Accession XM\_085627) is another VGAM892 host target gene. LOC146880 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC146880, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146880 BINDING SITE, desig-

nated SEQ ID:38258, to the nucleotide sequence of VGAM892 RNA, herein designated VGAM RNA, also designated SEQ ID:3603.

[33823] Another function of VGAM892 is therefore inhibition of LOC146880 (Accession XM\_085627). Accordingly, utilities of VGAM892 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146880. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 893 (VGAM893) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33824] VGAM893 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM893 was detected is described hereinabove with reference to Figs. 1–8.

[33825] VGAM893 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Periplaneta Fuliginosa Densovirus. VGAM893 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33826] VGAM893 gene encodes a VGAM893 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM893 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM893 precursor RNA is designated SEQ ID:879, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:879 is located at position 2 relative to the genome of *Periplaneta Fuliginosa* Densovirus.

[33827] VGAM893 precursor RNA folds onto itself, forming VGAM893 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33828] An enzyme complex designated DICER COMPLEX, `dices` the VGAM893 folded precursor RNA into VGAM893 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a



hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 61%) nucleotide sequence of VGAM893 RNA is designated SEQ ID:3604, and is provided hereinbelow with reference to the sequence listing part.

[33829] VGAM893 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM893 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM893 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33830] VGAM893 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM893 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM893 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM893 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM893 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33831] The complementary binding of VGAM893 RNA, herein designated VGAM RNA, to host target binding sites on VGAM893 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM893 host target RNA into VGAM893 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33832] It is appreciated that VGAM893 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM893 host target genes. The mRNA of each one of this plurality of VGAM893 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM893 RNA, herein designated VGAM RNA, and which when bound by VGAM893 RNA causes inhibition of translation of respective one or more VGAM893 host target proteins.

[33833] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM893 gene, herein designated VGAM GENE, on one or more VGAM893 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[33834] It is yet further appreciated that a function of VGAM893 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of viral infection by Periplaneta Fuliginosa Densovirus. Specific functions, and accordingly utilities, of VGAM893 correlate with, and may be deduced from, the identity of the host target genes which VGAM893 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33835] Nucleotide sequences of the VGAM893 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM893 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM893 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM893 are further described hereinbelow with reference to Table 1.

[33836] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM893 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM893 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33837] As mentioned hereinabove with reference to Fig. 1, a function of VGAM893 gene, herein designated VGAM is inhibition of expression of VGAM893 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM893 correlate with, and may be deduced from, the identity of the target genes which VGAM893 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33838] Cadherin, EGF LAG Seven-pass G-type Receptor 3 (flamingo homolog, Drosophila) (CELSR3, Accession NM\_001407) is a VGAM893 host target gene. CELSR3 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CELSR3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CELSR3 BINDING SITE, designated SEQ ID:7104, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33839] A function of VGAM893 is therefore inhibition of Cadherin, EGF LAG Seven-pass G-type Receptor 3 (flamingo homolog, *Drosophila*) (CELSR3, Accession NM\_001407), a gene which interacts in a homophilic manner in connecting cells. Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CELSR3. The function of CELSR3 has been established by previous studies. The domain that characterizes epidermal growth factor (EGF; 131530) consists of approximately 50 amino acids with 3 disulfide bonds. EGF-like domains are believed to play a critical role in a number of extracellular events, including cell adhesion and receptor-ligand interactions. Proteins with EGF-like domains often consist of more than 1,000 amino acids, have multiple copies of the EGF-like domain, and contain additional domains known to be involved in specific protein-protein interactions. To identify proteins containing EGF-like domains, Nakayama et al. (1998) searched a database of long cDNA sequences randomly selected from a human brain cDNA library for those that encode an EGF-like motif. They identified several partial cDNAs encoding novel proteins with EGF-like domains, such as EGFL1, which they named MEGF2. Nakayama et al.

(1998) isolated a rat cDNA containing the complete Megf2 coding sequence. The predicted Megf2 protein has a signal sequence, 8 cadherin motifs (see OMIM Ref. No. 603006), 6 EGF-like domains, 2 laminin G domains (see OMIM Ref. No. 601033), 7 transmembrane domains, and a cytoplasmic proline-rich sequence. Megf2 appears to have a domain structure identical to that of human MEGF3 (OMIM Ref. No. 604265), whose partial cDNA was also isolated by the authors. Northern blot analysis detected Megf2 expression in several regions of rat brain.

[33840] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33841] Nakayama, M.; Nakajima, D.; Nagase, T.; Nomura, N.; Seki, N.; Ohara, O. : Identification of high-molecular-weight proteins with multiple EGF-like motifs by motif-trap screening. Genomics 51: 27-34, 1998. ; and

[33842] Wu, Q.; Maniatis, T. : Large exons encoding multiple ectodomains are a characteristic feature of protocadherin genes. Proc. Nat. Acad. Sci. 97: 3124-3129, 2000.

[33843] Further studies establishing the function and utilities of CELSR3 are found in John Hopkins OMIM database record ID 604264, and in cited publications numbered

7437–7438 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DXS1283E (Accession XM\_047871) is another VGAM893 host target gene. DXS1283E BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DXS1283E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DXS1283E BINDING SITE, designated SEQ ID:35069, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33844] Another function of VGAM893 is therefore inhibition of DXS1283E (Accession XM\_047871). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DXS1283E. Potassium Voltage-gated Channel, Shaker-related Subfamily, Member 6 (KCNA6, Accession NM\_002235) is another VGAM893 host target gene. KCNA6 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KCNA6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.



Table 2 illustrates the complementarity of the nucleotide sequences of KCNA6 BINDING SITE, designated SEQ ID:8018, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33845] Another function of VGAM893 is therefore inhibition of Potassium Voltage-gated Channel, Shaker-related Subfamily, Member 6 (KCNA6, Accession NM\_002235), a gene which mediates the voltage-dependent potassium ion permeability of excitable membranes. Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KCNA6. The function of KCNA6 has been established by previous studies. By screening a human fetal cDNA library with a rat RCK3 potassium channel cDNA, Grupe et al. (1990) isolated cDNAs encoding a protein that they designated HBK2 (human brain potassium channel-2). The authors also cloned cDNAs corresponding to the rat homolog, RCK2. The predicted 529-amino acid HBK2 protein shares 94% identity with RCK2. HBK2 and RCK2 have the characteristic structure of voltage-gated ionic channels, with 6 potential membrane-spanning segments. When expressed in *Xenopus* oocytes, the HBK2/RCK2 channels ex-

hibited the functional characteristics of a delayed-rectifier channel that acts especially in the more positive membrane voltage range. The functional and pharmacologic properties of HBK2/RCK2 potassium channels were distinct from those of previously characterized channels.

Grupe et al. (1990) determined that the HBK2 gene did not contain introns. Using interspecific backcrosses between *Mus musculus* and *Mus spretus*, Klocke et al. (1993) mapped the mouse gene encoding the Kv1.6 potassium voltage-gated channel, *Kcna6*, to chromosome 6 in a cluster with *Kcna1*, *Kcna5* (OMIM Ref. No. 176267), and the homolog of human TPI1 (OMIM Ref. No. 190450).

Since human TPI1 is located on band 12p13, Klocke et al. (1993) predicted that the human KCNA6 gene is located on 12p near other genes of the Shaker-related subfamily, KCNA1 and KCNA5. Albrecht et al. (1995) determined that a 300-kb cluster on chromosome 12p13 contains the human KCNA6, KCNA1, and KCNA5 genes arranged in tandem

[33846] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33847] Albrecht, B.; Weber, K.; Pongs, O. : Characterization of a

voltage-activated K-channel gene cluster on human chromosome 12p13. Receptors Channels 3: 213-220, 1995. ; and

[33848] Grupe, A.; Schroter, K. H.; Ruppertsberg, J. P.; Stocker, M.; Drewes, T.; Beckh, S.; Pongs, O. : Cloning and expression of a human voltage-gated potassium channel: a novel member of the R.

[33849] Further studies establishing the function and utilities of KCNA6 are found in John Hopkins OMIM database record ID 176257, and in cited publications numbered 10288-10290 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Spinocerebellar Ataxia 1 (olivopontocerebellar ataxia 1, autosomal dominant, ataxin 1) (SCA1, Accession NM\_000332) is another VGAM893 host target gene. SCA1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SCA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCA1 BINDING SITE, designated SEQ ID:5881, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33850] Another function of VGAM893 is therefore inhibition of Spinocerebellar Ataxia 1 (olivopontocerebellar ataxia 1, autosomal dominant, ataxin 1) (SCA1, Accession NM\_000332). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SCA1. Ganglioside Induced Differentiation Associated Protein 2 (GDAP2, Accession NM\_017686) is another VGAM893 host target gene. GDAP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GDAP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GDAP2 BINDING SITE, designated SEQ ID:19240, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33851] Another function of VGAM893 is therefore inhibition of Ganglioside Induced Differentiation Associated Protein 2 (GDAP2, Accession NM\_017686). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GDAP2. KIAA1708 (Accession XM\_040211) is another VGAM893

host target gene. KIAA1708 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1708, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1708 BINDING SITE, designated SEQ ID:33273, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33852] Another function of VGAM893 is therefore inhibition of KIAA1708 (Accession XM\_040211). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1708. MRF2 (Accession XM\_084482) is another VGAM893 host target gene. MRF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MRF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MRF2 BINDING SITE, designated SEQ ID:37602, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33853] Another function of VGAM893 is therefore inhibition of MRF2 (Accession XM\_084482). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MRF2. PHD Finger Protein 5A (PHF5A, Accession NM\_032758) is another VGAM893 host target gene. PHF5A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PHF5A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PHF5A BINDING SITE, designated SEQ ID:26502, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33854] Another function of VGAM893 is therefore inhibition of PHD Finger Protein 5A (PHF5A, Accession NM\_032758). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PHF5A. SERP1 (Accession NM\_014445) is another VGAM893 host target gene. SERP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SERP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BIND-

ING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SERP1 BINDING SITE, designated SEQ ID:15796, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33855] Another function of VGAM893 is therefore inhibition of SERP1 (Accession NM\_014445). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SERP1. LOC153196 (Accession XM\_098323) is another VGAM893 host target gene. LOC153196 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC153196, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153196 BINDING SITE, designated SEQ ID:41595, to the nucleotide sequence of VGAM893 RNA, herein designated VGAM RNA, also designated SEQ ID:3604.

[33856] Another function of VGAM893 is therefore inhibition of LOC153196 (Accession XM\_098323). Accordingly, utilities of VGAM893 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC153196. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 894 (VGAM894) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33857] VGAM894 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM894 was detected is described hereinabove with reference to Figs. 1–8.

[33858] VGAM894 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Periplaneta Fuliginosa Densovirus. VGAM894 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33859] VGAM894 gene encodes a VGAM894 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM894 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM894 precursor RNA is designated SEQ ID:880, and is provided hereinbelow with reference to the



sequence listing part. Nucleotide sequence SEQ ID:880 is located at position 2107 relative to the genome of Periplaneta Fuliginosa Densovirus.

[33860] VGAM894 precursor RNA folds onto itself, forming VGAM894 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33861] An enzyme complex designated DICER COMPLEX, `dices` the VGAM894 folded precursor RNA into VGAM894 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM894 RNA is designated SEQ ID:3605, and is provided hereinbelow with reference to the sequence listing part.

[33862] VGAM894 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM894 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM894 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33863] VGAM894 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM894 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM894 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM894 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in

untranslated regions of a VGAM894 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[33864] The complementary binding of VGAM894 RNA, herein designated VGAM RNA, to host target binding sites on VGAM894 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM894 host target RNA into VGAM894 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33865] It is appreciated that VGAM894 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM894 host target genes. The mRNA of each one of this plurality of VGAM894 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM894 RNA, herein designated VGAM RNA, and which when bound by VGAM894 RNA causes in-

hibition of translation of respective one or more VGAM894 host target proteins.

[33866] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM894 gene, herein designated VGAM GENE, on one or more VGAM894 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33867] It is yet further appreciated that a function of VGAM894 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM894 include diagnosis, prevention and

treatment of viral infection by *Periplaneta Fuliginosa* Densovirus. Specific functions, and accordingly utilities, of VGAM894 correlate with, and may be deduced from, the identity of the host target genes which VGAM894 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33868] Nucleotide sequences of the VGAM894 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM894 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM894 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM894 are further described hereinbelow with reference to Table 1.

[33869] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM894 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM894 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33870] As mentioned hereinabove with reference to Fig. 1, a function of VGAM894 gene, herein designated VGAM is inhibition of expression of VGAM894 target genes. It is

appreciated that specific functions, and accordingly utilities, of VGAM894 correlate with, and may be deduced from, the identity of the target genes which VGAM894 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33871] A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 3 (ADAMTS3, Accession NM\_014243) is a VGAM894 host target gene. ADAMTS3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAMTS3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAMTS3 BINDING SITE, designated SEQ ID:15510, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33872] A function of VGAM894 is therefore inhibition of A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 3 (ADAMTS3, Accession NM\_014243), a gene which cleaves the propeptides of type ii collagen prior to fibril assembly. Accordingly, utilities of VGAM894 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with ADAMTS3. The function of ADAMTS3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM211. Chromosome 8 Open Reading Frame 1 (C8orf1, Accession NM\_004337) is another VGAM894 host target gene. C8orf1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C8orf1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C8orf1 BINDING SITE, designated SEQ ID:10533, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33873] Another function of VGAM894 is therefore inhibition of Chromosome 8 Open Reading Frame 1 (C8orf1, Accession NM\_004337). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C8orf1. Cyclin-dependent Kinase Inhibitor 2A (melanoma, p16, inhibits CDK4) (CDKN2A, Accession NM\_058197) is another VGAM894 host target gene. CDKN2A BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by CDKN2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDKN2A BINDING SITE, designated SEQ ID:27760, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33874] Another function of VGAM894 is therefore inhibition of Cyclin-dependent Kinase Inhibitor 2A (melanoma, p16, inhibits CDK4) (CDKN2A, Accession NM\_058197). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDKN2A. Crystallin, Zeta (quinone reductase) (CRYZ, Accession NM\_001889) is another VGAM894 host target gene. CRYZ BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CRYZ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CRYZ BINDING SITE, designated SEQ ID:7617, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ



ID:3605.

[33875] Another function of VGAM894 is therefore inhibition of Crystallin, Zeta (quinone reductase) (CRYZ, Accession NM\_001889), a gene which may act in the detoxification of xenobiotics. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CRYZ. The function of CRYZ and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM323.Cytochrome P450, Subfamily I (dioxin-inducible), Polypeptide 1 (glaucoma 3, primary infantile) (CYP1B1, Accession NM\_000104) is another VGAM894 host target gene. CYP1B1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP1B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP1B1 BINDING SITE, designated SEQ ID:5568, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33876] Another function of VGAM894 is therefore inhibition of

Cytochrome P450, Subfamily I (dioxin-inducible), Polypeptide 1 (glaucoma 3, primary infantile) (CYP1B1, Accession NM\_000104), a gene which participates in the metabolism of a molecule that is a participant in eye development. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP1B1. The function of CYP1B1 has been established by previous studies. In the study of candidate genes identified in the critical region of 2p21 where a major gene for primary congenital glaucoma, GLC3A (OMIM Ref. No. 231300), had been mapped by linkage studies, Stoilov et al. (1997) found the CYP1B1 gene, which had previously been identified by Sutter et al. (1994). From a determination of the intron/exon junctions of this gene, Stoilov et al. (1997) concluded that the gene contains 3 exons and 2 introns. The entire coding sequence of the genes is contained in exons 2 and 3. This genomic structure agreed with that reported by Tang et al. (1996). Screening for the presence of coding sequence changes in the CYP1B1 gene, Stoilov et al. (1997) identified 3 different truncating mutations: a 13-bp deletion found in 1 consanguineous and 1 nonconsanguineous family (601771.0001); a single cytosine insertion ob-

served in another 2 consanguineous families (601771.0002); and a large deletion found in an additional consanguineous family. In addition, a G-to-C transversion at nucleotide 1640 of the CYP1B1 coding sequence was found that caused a val432-to-leu amino acid substitution. This change created an EcoR57 restriction site, thus providing a rapid screening method. Heterozygosity for the val432-to-leu change was found in 51.4% of 70 normal individuals. This amino acid change was not in that part of CYP1B1 that represented conserved sequences, and both valine and leucine are neutral and hydrophobic. Their very similar aliphatic side groups differ by a single -CH<sub>2</sub> group. Therefore, this change appeared to represent a common amino acid polymorphism that is not related to the primary congenital glaucoma phenotype. Identification of CYP1B1 as the gene affected in primary congenital glaucoma was said by Stoilov et al. (1997) to be the first example in which mutations in a member of the cytochrome P450 superfamily results in a primary developmental defect. The finding was not unexpected, however, as a link between members of this superfamily and the processes of growth and differentiation had been postulated previously. They speculated that CYP1B1 par-

ticipates in the metabolism of an as-yet-unknown biologically active molecule that is a participant in eye development. Stoilov et al. (1997) demonstrated that a stable protein product is produced in the affected subjects of these families, and that the 3 mutations they described would be expected to result in a product lacking between 189 and 254 amino acids from the C terminus. This segment harbors the invariant cysteine of all known cytochrome P450 amino sequences; in CYP1B1 it is cys470. Schwartzman et al. (1987) implicated a cytochrome-P450-dependent arachidonate metabolite that inhibits Na<sup>+</sup>,K<sup>+</sup>-ATPase in the cornea in regulating corneal transparency and aqueous humor secretion. This finding is consistent with the clouding of the cornea and increased intraocular pressure, the 2 major diagnostic criteria for primary congenital glaucoma.

[33877] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33878] Bejjani, B. A.; Lewis, R. A.; Tomey, K. F.; Anderson, K. L.; Dueker, D. K.; Jabak, M.; Astle, W. F.; Otterud, B.; Leppert, M.; Lupski, J. R. : Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary

congenital glaucoma in Saudi Arabia. Am. J. Hum. Genet. 62: 325–333, 1998. ; and

[33879] Stoilov, I.; Akarsu, A. N.; Alozie, I.; Child, A.; Barsoum–Homsy, M.; Turacli, M. E.; Or, M.; Lewis, R. A.; Ozdemir, N.; Brice, G.; Aktan, S. G.; Chevrette, L.; Coca–Prados, M.; Sarfara.

[33880] Further studies establishing the function and utilities of CYP1B1 are found in John Hopkins OMIM database record ID 601771, and in cited publications numbered 8866–8867, 911 and 9123–9129 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Forkhead Box P2 (FOXP2, Accession NM\_014491) is another VGAM894 host target gene. FOXP2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FOXP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FOXP2 BINDING SITE, designated SEQ ID:15835, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33881] Another function of VGAM894 is therefore inhibition of

Forkhead Box P2 (FOXP2, Accession NM\_014491), a gene which may have a role in regulating neurodevelopment or neuroplasticity. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FOXP2. The function of FOXP2 has been established by previous studies. In a search for the gene responsible for the severe speech and language disorder (OMIM Ref. No. 602081) in the KE pedigree, Lai et al. (2001) isolated the FOXP2 gene. FOXP2 has an open reading frame (ORF) of 2.1 kb. The carboxy-terminal portion of the predicted protein sequence encoded by the FOXP2 gene contains a segment of 84 amino acids (encoded by exons 12–14) that shows high similarity to the characteristic DNA-binding domains of the forkhead-winged helix (FOX) family of transcription factors. By Northern blot analysis of several human adult tissues, Lai et al. (2001) demonstrated broad expression of a roughly 6.5-kb FOXP2 transcript. This transcript was also observed in fetal tissues, with strong expression in brain. A murine homolog of FOXP2 is expressed in adult and fetal mouse brain. The FOXP2 gene is mutated in a severe monogenic form of speech and language impairment, segregating within a single large pedigree, and is also

disrupted by a translocation in an isolated case. Several studies of autistic disorder have demonstrated linkage to a similar region of 7q (AUTS1; 209850), leading to the proposal that a single genetic factor on 7q31 contributes to both autism and language disorders. Newbury et al. (2002) used association and mutation screening analyses to evaluate directly the impact of the FOXP2 gene with regard to both complex language impairments and autism. They concluded that the coding region variants in FOXP2 do not underlie the AUTS1 linkage and that the gene is unlikely to play a role in autism or more common forms of language impairment.

[33882] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33883] Lai, C. S. L.; Fisher, S. E.; Hurst, J. A.; Levy, E. R.; Hodgson, S.; Fox, M.; Jeremiah, S.; Povey, S.; Jamison, D. C.; Green, E. D.; Vargha-Khadem, F.; Monaco, A. P. : The SPCH1 region on human 7q31: genomic characterization of the critical interval and localization of translocations associated with speech and language disorder. *Am. J. Hum. Genet.* 67: 357–368, 2000. ; and

[33884] Newbury, D. F.; Bonora, E.; Lamb, J. A.; Fisher, S. E.; Lai, C.

S. L.; Baird, G.; Jannoun, L.; Slonims, V.; Stott, C. M.; Mericks, M. J.; Bolton, P. F.; Bailey, A. J.; Monaco, A. P.;

[33885] Further studies establishing the function and utilities of FOXP2 are found in John Hopkins OMIM database record ID 605317, and in cited publications numbered 4483–4484, 5967–596 and 8561 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Interleukin 18 Receptor 1 (IL18R1, Accession NM\_003855) is another VGAM894 host target gene. IL18R1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL18R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL18R1 BINDING SITE, designated SEQ ID:9952, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33886] Another function of VGAM894 is therefore inhibition of Interleukin 18 Receptor 1 (IL18R1, Accession NM\_003855), a gene which is required for dorsal–ventral embryonic polarity and promotes heterophilic cellular adhesion. Accordingly, utilities of VGAM894 include diagno–



sis, prevention and treatment of diseases and clinical conditions associated with IL18R1. The function of IL18R1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM37.Meis1, Myeloid Ecotropic Viral Integration Site 1 Homolog (mouse) (MEIS1, Accession NM\_002398) is another VGAM894 host target gene. MEIS1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MEIS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MEIS1 BINDING SITE, designated SEQ ID:8219, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33887] Another function of VGAM894 is therefore inhibition of Meis1, Myeloid Ecotropic Viral Integration Site 1 Homolog (mouse) (MEIS1, Accession NM\_002398), a gene which may regulate gene expression and control cell differentiation. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEIS1. The function of MEIS1 has

been established by previous studies. Homeo box genes, of which the most well-characterized category is represented by the HOX genes, play a crucial role in normal development. In addition, several homeoproteins are involved in neoplasia: PPX1 (OMIM Ref. No. 176310), HOXA10 (OMIM Ref. No. 142957), and HOXB8 (OMIM Ref. No. 142963) play important roles in leukemia. The Meis1 locus was isolated by Moskow et al. (1995) as a common site of viral integration involved in myeloid leukemia in BXH-2 mice. MEIS1 encodes a novel homeo box protein belonging to the TALE (three amino acid loop extension) family of homeodomain-containing proteins. The homeodomain of MEIS1 is the only conserved motif within the entire 390-amino acid protein. Steelman et al. (1997) described additional members of a related gene family, which they called Meis1-related genes (MRGs; OMIM Ref. No. 601740). Mercader et al. (1999) described the role of homeo box genes Meis1, Meis2, and Pbx1 in the development of mouse, chicken, and Drosophila limbs. Mercader et al. (1999) found that Meis1 and Meis2 expression is restricted to the proximal domain, coincident with the previously reported domain in which Pbx1 is localized to the nucleus. Meis1 regulates Pbx1 activity by promoting nu-

clear import of the Pbx1 protein. Mercader et al. (1999) also demonstrated that ectopic expression of Meis1 in chicken disrupts distal limb development and induces distal-to-proximal transformations. Mercader et al. (1999) concluded that the restriction of Meis1 to proximal regions of the vertebrate limb is essential to specify cell fates and differentiation patterns along the proximodistal axis of the limb. Thorsteinsdottir et al. (2001) identified MEIS1 as a common collaborator with 2 divergent HOX genes, HOXA9 (OMIM Ref. No. 142956) and HOXB3 (OMIM Ref. No. 142966), in leukemic transformation. Using over-expression studies in bone marrow cells, they also demonstrated that each HOX gene studied predisposes to leukemias that are phenotypically distinct and that MEIS1 acts primarily to accelerate the occurrence of these leukemias without altering their phenotype. By fluorescence in situ hybridization, Moskow et al. (1995) mapped the human MEIS1 gene to 2p14-p13 near 3 translocation breakpoints involved in human leukemia. They mapped the murine homolog to mouse 11.

[33888] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [33889] Moskow, J. J.; Bullrich, F.; Huebner, K.; Daar, I. O.; Buchberg, A. M. : Meis1, a PBX1-related homeobox gene involved in myeloid leukemia in BXH-2 mice. *Molec. Cell. Biol.* 15: 5434-5443, 1995. ; and
- [33890] Steelman, S.; Moskow, J. J.; Muzynski, K.; North, C.; Druck, T.; Montgomery, J. C.; Huebner, K.; Daar, I. O.; Buchberg, A. M. : Identification of a conserved family of Meis1-related home.
- [33891] Further studies establishing the function and utilities of MEIS1 are found in John Hopkins OMIM database record ID 601739, and in cited publications numbered 10366-9328 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. N-acetylgalactosaminidase, Alpha- (NAGA, Accession NM\_000262) is another VGAM894 host target gene. NAGA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NAGA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAGA BINDING SITE, designated SEQ ID:5803, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33892] Another function of VGAM894 is therefore inhibition of N-acetylgalactosaminidase, Alpha- (NAGA, Accession NM\_000262). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAGA. Phosphoribosylaminoimidazole Carboxylase, Phosphoribosylaminoimidazole Succinocarboxamide Synthetase (PAICS, Accession NM\_006452) is another VGAM894 host target gene. PAICS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAICS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAICS BINDING SITE, designated SEQ ID:13166, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33893] Another function of VGAM894 is therefore inhibition of Phosphoribosylaminoimidazole Carboxylase, Phosphoribosylaminoimidazole Succinocarboxamide Synthetase (PAICS, Accession NM\_006452), a gene which is required for purine biosynthesis. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAICS. The function

of PAICS has been established by previous studies. Schild et al. (1990) used the functional complementation of mutations in *Saccharomyces cerevisiae* to isolate a human cDNA clone complementing the ade-2 (phosphoribosylaminoimidazole carboxylase; EC 4.1.1.21) yeast mutation. The same cDNA also complemented ade-1 (phosphoribosylaminoimidazole succinocarboxamide synthetase; EC 6.3.2.6); thus, this is a bifunctional enzyme. Although these enzymes are encoded by genes on different chromosomes in yeast, their enzymatic activities copurify from chicken livers, and the complementation of both activities by this single cDNA clone suggests that the enzyme is bifunctional in humans. Barton et al. (1991) mapped the gene to chromosome 4 by fusing Chinese hamster ovary (CHO) cells carrying the Ade(-)D mutation with human lymphocytes using inactivated Sendai virus. Two of the isolated subclones contained only the long arm of human chromosome 4 translocated onto a CHO chromosome, thus providing evidence that the gene in question is on 4q. By subjecting 2 of the subclones containing chromosome 4 to BrdU visible light segregation, Barton et al. (1991) demonstrated that all of the isolated purine auxotrophic cell lines showed a loss of 4q. It is noteworthy

thy that this bifunctional enzyme maps to the same general region as the monofunctional enzyme PPAT (OMIM Ref. No. 172450), which catalyzes the first step in the biosynthetic pathway for the production of AMP from phosphoribosylpyrophosphate (PRPP) and maps to 4pter-q21. AIR carboxylase (EC 4.1.1.21)/SAICAR synthetase (EC 6.3.2.6) is a bifunctional enzyme, the activities of which are required for steps 6 and 7, respectively, of purine biosynthesis. Brayton et al. (1994) demonstrated that in the human, as in the chicken, the GPAT gene (OMIM Ref. No. 172450), which catalyzes the first and presumably rate-limiting reaction in purine biosynthesis, is closely linked and divergently transcribed. The intergenic region is approximately 625 bp in the human and 229 bp in the chicken. Although there are several examples for bidirectional transcription in higher eukaryotes, GPAT-AIRC was the first example for bidirectional transcription of tightly coupled genes that are not structurally related but are involved in the same pathway. This may be a eukaryotic equivalent of a prokaryotic operon.

[33894] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [33895] Schild, D.; Brake, A. J.; Kiefer, M. C.; Young, D.; Barr, P. J. : Cloning of three human multifunctional de novo purine biosynthetic genes by functional complementation of yeast mutations. *Proc. Nat. Acad. Sci.* 87: 2916–2920, 1990. ; and
- [33896] Brayton, K. A.; Chen, Z.; Zhou, G.; Nagy, P. L.; Gavalas, A.; Trent, J. M.; Deaven, L. L.; Dixon, J. E.; Zalkin, H. : Two genes for de novo purine nucleotide synthesis on human chromosom.
- [33897] Further studies establishing the function and utilities of PAICS are found in John Hopkins OMIM database record ID 172439, and in cited publications numbered 10941–1094 and 4809 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Protein Phosphatase 2, Regulatory Subunit B (B56), Delta Isoform (PPP2R5D, Accession NM\_006245) is another VGAM894 host target gene. PPP2R5D BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by PPP2R5D, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R5D BINDING SITE, designated SEQ ID:12919, to the nucleotide sequence of



VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33898] Another function of VGAM894 is therefore inhibition of Protein Phosphatase 2, Regulatory Subunit B (B56), Delta Isoform (PPP2R5D, Accession NM\_006245), a gene which is a regulatory subunit of protein phosphatase 2A. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R5D. The function of PPP2R5D and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM96.SH2 Domain Protein 1A, Duncan's Disease (lymphoproliferative syndrome) (SH2D1A, Accession NM\_002351) is another VGAM894 host target gene. SH2D1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SH2D1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SH2D1A BINDING SITE, designated SEQ ID:8156, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33899] Another function of VGAM894 is therefore inhibition of SH2 Domain Protein 1A, Duncan's Disease (lymphoproliferative syndrome) (SH2D1A, Accession NM\_002351), a gene which is involved in t cell signaling. inhibits slam self-association. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SH2D1A. The function of SH2D1A has been established by previous studies. Sumegi et al. (2000) reported that analysis of 35 families from the XLP Registry revealed 28 different mutations in 34 families: 3 large genomic deletions, 10 small intragenic deletions, 3 splice site, 3 nonsense, and 9 missense mutations. No mutations were found in 25 males, so-called sporadic XLP (males with an XLP phenotype after EBV infection but no family history of XLP), or in 9 patients with chronic active EBV syndrome. The authors found that although EBV infection often resulted in fulminant infectious mononucleosis, it was not necessary for the expression of other manifestations of XLP and correlated poorly with outcome. They interpreted the results as suggesting that unidentified factors, either environmental or genetic (e.g., modifier genes), contribute to the pathogenesis of XLP. Animal model experiments lend further support to

the function of SH2D1A. Wu et al. (2001) generated Sap-deficient mice, which were fertile and had no defects in lymphocyte surface markers or overall morphology. Sap-deficient mice had increased lymphocytic choriomeningitis virus (LCMV)-specific splenic and hepatic T cells and increased gamma-interferon (IFNG; 147570) production compared with their wildtype littermates. All Sap-deficient mice died as a result of hepatotropic LCMV infection, while only 30% of wildtype mice died. In contrast to the increased Ifng production, interleukin-4 (IL4; 147780) production was markedly lower in Sap-deficient mice. Mice with a BALB/c background are normally highly susceptible to infection with the Leishmania major parasite due to poor Ifng production. However, Sap-deficient mice with a BALB/c background produced little Il4 and high levels of Ifng and had lower parasite burdens than wildtype BALB/c mice. This suggested that in the absence of SAP, IL4 gene activation is defective. Lower Il4 expression in Sap-deficient mice correlated with greatly reduced IgE production and reduced basal IgE expression. Wu et al. (2001) proposed that the Sap-deficient mouse model would be a useful tool for dissecting the complex XLP phenotypes.

[33900] It is appreciated that the abovementioned animal model for SH2D1A is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications sited hereinbelow.

[33901] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33902] Sumegi, J.; Huang, D.; Lanyi, A.; Davis, J. D.; Seemayer, T. A.; Maeda, A.; Klein, G.; Seri, M.; Wakiguchi, H.; Purtilo, D. T.; Gross, T. G. : Correlation of mutations of the SH2D1A gene and Epstein–Barr virus infection with clinical phenotype and outcome in X–linked lymphoproliferative disease. Blood 96: 3118–3125, 2000. ; and

[33903] Wu, C.; Nguyen, K. B.; Pien, G. C.; Wang, N.; Gullo, C.; Duncan, H.; Sosa, M. R.; Edwards, M. J.; Borrow, P.; Satoskar, A. R.; Sharpe, A. H.; Biron, C. A.; Terhorst, C. : SAP controls T c.

[33904] Further studies establishing the function and utilities of SH2D1A are found in John Hopkins OMIM database record ID 308240, and in sited publications numbered 8594–8597, 8599, 8600–8612, 4213, 8056–8071, 9435–8079, 8770–123 and 8771–8781 listed in the bibliography section hereinbelow, which are also hereby incor–

porated by reference. Solute Carrier Family 21 (organic anion transporter), Member 9 (SLC21A9, Accession NM\_007256) is another VGAM894 host target gene. SLC21A9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC21A9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC21A9 BINDING SITE, designated SEQ ID:14127, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33905] Another function of VGAM894 is therefore inhibition of Solute Carrier Family 21 (organic anion transporter), Member 9 (SLC21A9, Accession NM\_007256), a gene which is Moderately similar to SLC21A2 prostaglandin transporter. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC21A9. The function of SLC21A9 has been established by previous studies. By screening human brain cDNAs for the potential to encode proteins that are at least 50 kD, Nagase et al. (1998) isolated an SLC21A9 cDNA, which they called KIAA0880, that

contains a complete coding sequence. The predicted 709-amino acid SLC21A9 protein contains 8 membrane-spanning regions. SLC21A9 shares 42.8% amino acid sequence identity with a rat prostaglandin transporter across 678 residues. RT-PCR followed by ELISA detected SLC21A9 expression in all human tissues examined, with the highest expression in liver, lower expression in lung, ovary, brain, heart, kidney, pancreas, spleen, and testis, and lowest expression in skeletal muscle. Organic anion-transporting polypeptides (OATPs) are a family of multi-specific carriers that mediate the sodium-independent transport of steroid hormone and conjugates, drugs, and numerous anionic endogenous substrates. St-Pierre et al. (2002) investigated whether members of the OATP gene family could mediate fetal-maternal transfer of anionic steroid conjugates in the human placenta. They isolated OATPB (SLC21A9) from a placenta cDNA library. An anti-serum to OATPB detected an 85-kD protein in basal but not apical syncytiotrophoblast membranes. Immunohistochemistry of first-, second-, and third-trimester placenta showed staining in the cytotrophoblast membranes and at the basal surface of the syncytiotrophoblast. Trophoblasts that reacted with an antibody to Ki-67, a proliferation-as-

sociated antigen, expressed lower levels of OATPB. OATPB mRNA levels were measured in isolated trophoblasts under culture conditions that promoted syncytia formation. Real-time quantitative PCR estimated an 8-fold increase in OATPB expression on differentiation to syncytia. Pregnenolone sulfate partially inhibited OATPB-mediated transport of estrone-3-sulfate in an oocyte expression system. The authors concluded that these findings suggested a physiologic role for OATPB in the placental uptake of fetal-derived sulfated steroids

[33906] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33907] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Hiro-sawa, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. XII. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. DNA Res. 5: 355-364, 1998. ; and

[33908] St-Pierre, M. V.; Hagenbuch, B.; Ugele, B.; Meier, P. J.; Stallmach, T. : Characterization of an organic anion-transporting polypeptide (OATP-B) in human placenta. J. Clin. Endocr. Metab.

[33909] Further studies establishing the function and utilities of SLC21A9 are found in John Hopkins OMIM database record ID 604988, and in cited publications numbered 493 and 7097 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Transcriptional Adaptor 2 (ADA2 homolog, yeast)-like (TADA2L, Accession NM\_001488) is another VGAM894 host target gene. TADA2L BINDING SITE1 and TADA2L BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by TADA2L, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TADA2L BINDING SITE1 and TADA2L BINDING SITE2, designated SEQ ID:7229 and SEQ ID:28520 respectively, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33910] Another function of VGAM894 is therefore inhibition of Transcriptional Adaptor 2 (ADA2 homolog, yeast)-like (TADA2L, Accession NM\_001488), a gene which is one PCAF histone acetylase complex subunit, and a probable transcriptional adaptor protein. Accordingly, utilities of



VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TADA2L. The function of TADA2L has been established by previous studies. The ability of DNA-bound transcriptional activator proteins to enhance the initiation rate of RNA polymerase II-mediated gene transcription hinges on their potential to interact functionally with the general transcription machinery bound at the basal promoter. Candau et al. (1996) identified expressed sequence tags of possible human homologs of the yeast transcriptional activator proteins ADA2 and GCN5. Full-length cDNAs, designated TADA2L and GCN5L2 (OMIM Ref. No. 602301), were isolated from testis. The predicted 443-amino acid TADA2L protein is 31% identical to the yeast ADA2 protein.

TADA2L was shown to function experimentally as an adaptor in a human cell line. Carter et al. (1997) found that TADA2L is transcribed to varying degrees in all tissue types, but most abundantly in testis. By fluorescence in situ hybridization, they mapped the TADA2L gene to 17q12-q21, proximal to GCN5L2. Ogryzko et al. (1998) found that TADA2L is associated with the P/CAF (OMIM Ref. No. 602303) protein in the PCAF complex. Struhl and Moqtaderi (1998) reviewed the potential roles of the PCAF

complex in transcription.

[33911] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33912] Carter, K. C.; Wang, L.; Shell, B. K.; Zamir, I.; Berger, S. L.; Moore, P. A. : The human transcriptional adaptor genes TADA2L and GCN5L2 colocalize to chromosome 17q12-q21 and display a similar tissue expression pattern. Genomics 40: 497-500, 1997. ; and

[33913] Ogryzko, V. V.; Kotani, T.; Zhang, X.; Schiltz, R. L.; Howard, T.; Yang, X.-J.; Howard, B. H.; Qin, J.; Nakatani, Y. : Histone-like TAFs within the PCAF histone acetylase complex. Cell.

[33914] Further studies establishing the function and utilities of TADA2L are found in John Hopkins OMIM database record ID 602276, and in cited publications numbered 2799-2802 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. TRIP15 (Accession NM\_004236) is another VGAM894 host target gene. TRIP15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIP15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of TRIP15 BINDING SITE, designated SEQ ID:10432, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33915] Another function of VGAM894 is therefore inhibition of TRIP15 (Accession NM\_004236), a gene which is a subunit of the COP9 signalosome complex. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIP15. The function of TRIP15 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM452. Ubiquitin Specific Protease 9, Y Chromosome (fat facets-like Drosophila) (USP9Y, Accession XM\_034147) is another VGAM894 host target gene. USP9Y BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by USP9Y, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of USP9Y BINDING SITE, designated SEQ ID:32019, to the nucleotide sequence of VGAM894 RNA, herein designated

VGAM RNA, also designated SEQ ID:3605.

[33916] Another function of VGAM894 is therefore inhibition of Ubiquitin Specific Protease 9, Y Chromosome (fat facets-like *Drosophila*) (USP9Y, Accession XM\_034147), a gene which removes ubiquitin from ubiquitin-conjugated proteins and has a role in spermatogenesis. Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with USP9Y. The function of USP9Y has been established by previous studies. Sun et al. (1999) were the first to trace spermatogenic failure to a point mutation in a Y-linked gene or to a deletion of a single Y-linked gene. They sequenced the AZFa (see OMIM Ref. No. 415000) region of the Y chromosome and identified 2 functional genes previously described: USP9Y and DBY (OMIM Ref. No. 400010). Screening of the 2 genes in 576 infertile and 96 fertile men revealed several sequence variants, most of which appeared to be heritable and of little functional consequence. They found 1 de novo mutation in USP9Y: a 4-bp deletion in the splice donor site, causing an exon to be skipped and protein truncation. This mutation was present in a man with nonobstructive azoospermia, but was absent in his fertile brother, suggesting that the

USP9Y mutation caused spermatogenic failure. Sun et al. (1999) also identified a single gene deletion associated with spermatogenic failure, again involving USP9Y, by re-analyzing a published study. The coding regions of the DFFRY and DFFRX genes show 89% identity at the nucleotide level. In common with DFFRX, the potential amino acid sequence of DFFRY contains the conserved cysteine and histidine domains characteristic of ubiquitin C-terminal hydrolases. The human DFFRY mRNA is expressed in a wide range of adult and embryonic tissues, including testis, whereas the homologous mouse Dffry gene is expressed specifically in the testis. Brown et al. (1998) found that 3 azoospermic male patients had deletion of DFFRY from the Y chromosome. Two patients had a testicular phenotype that resembled Sertoli cell-only syndrome (see OMIM Ref. No. 305700), and the third had diminished spermatogenesis. In all 3 patients, the deletions extended from close to the 3-prime end into the gene, removing the entire coding sequence of DFFRY. Brown et al. (1998) showed that the mouse Dffry gene maps to the Sxr-b deletion interval on the shorter arm of the mouse Y chromosome and that its expression in mouse testis can first be detected between 7.5 and 10.5 days after birth when

type A and B spermatogonia and preleptotene and leptotene spermatocytes are present.

[33917] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[33918] Sun, C.; Skaletsky, H.; Birren, B.; Devon, K.; Tang, Z.; Silber, S.; Oates, R.; Page, D. C. : An azoospermic man with a de novo point mutation in the Y-chromosomal gene USP9Y. *Nature Genet.* 23: 429–432, 1999. ; and

[33919] Brown, G. M.; Furlong, R. A.; Sargent, C. A.; Erickson, R. P.; Longepied, G.; Mitchell, M.; Jones, M. H.; Hargreave, T. B.; Cooke, H. J.; Affara, N. A. : Characterisation of the coding.

[33920] Further studies establishing the function and utilities of USP9Y are found in John Hopkins OMIM database record ID 400005, and in cited publications numbered 8827–882 and 9087–8833 listed in the bibliography section herein–below, which are also hereby incorporated by reference. Zinc–fingers and Homeoboxes 1 (ZHX1, Accession NM\_007222) is another VGAM894 host target gene. ZHX1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZHX1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illus–

trates the complementarity of the nucleotide sequences of ZHX1 BINDING SITE, designated SEQ ID:14092, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33921] Another function of VGAM894 is therefore inhibition of Zinc-fingers and Homeoboxes 1 (ZHX1, Accession NM\_007222). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZHX1. Adaptor-related Protein Complex 3, Mu 2 Subunit (AP3M2, Accession NM\_006803) is another VGAM894 host target gene. AP3M2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AP3M2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP3M2 BINDING SITE, designated SEQ ID:13678, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33922] Another function of VGAM894 is therefore inhibition of Adaptor-related Protein Complex 3, Mu 2 Subunit (AP3M2, Accession NM\_006803). Accordingly, utilities of

VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP3M2. Chromosome 8 Open Reading Frame 17 (C8orf17, Accession NM\_020237) is another VGAM894 host target gene. C8orf17 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C8orf17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C8orf17 BINDING SITE, designated SEQ ID:21506, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33923] Another function of VGAM894 is therefore inhibition of Chromosome 8 Open Reading Frame 17 (C8orf17, Accession NM\_020237). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C8orf17. DKFZP434J1813 (Accession XM\_029798) is another VGAM894 host target gene. DKFZP434J1813 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434J1813, corresponding to a HOST TARGET binding site such as BINDING SITE



I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434J1813 BINDING SITE, designated SEQ ID:30950, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33924] Another function of VGAM894 is therefore inhibition of DKFZP434J1813 (Accession XM\_029798). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434J1813. FLJ10520 (Accession NM\_018124) is another VGAM894 host target gene. FLJ10520 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10520, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10520 BINDING SITE, designated SEQ ID:19908, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33925] Another function of VGAM894 is therefore inhibition of FLJ10520 (Accession NM\_018124). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10520.

FLJ13449 (Accession NM\_024546) is another VGAM894 host target gene. FLJ13449 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ13449, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13449 BINDING SITE, designated SEQ ID:23760, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33926] Another function of VGAM894 is therefore inhibition of FLJ13449 (Accession NM\_024546). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13449. FLJ13842 (Accession NM\_024645) is another VGAM894 host target gene. FLJ13842 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13842, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13842 BINDING SITE, designated SEQ ID:23930, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also desig-

nated SEQ ID:3605.

[33927] Another function of VGAM894 is therefore inhibition of FLJ13842 (Accession NM\_024645). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13842. Glia Maturation Factor, Beta (GMFB, Accession NM\_004124) is another VGAM894 host target gene. GMFB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GMFB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GMFB BINDING SITE, designated SEQ ID:10331, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33928] Another function of VGAM894 is therefore inhibition of Glia Maturation Factor, Beta (GMFB, Accession NM\_004124). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GMFB. HCA127 (Accession NM\_018684) is another VGAM894 host target gene. HCA127 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

HCA127, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCA127 BINDING SITE, designated SEQ ID:20761, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33929] Another function of VGAM894 is therefore inhibition of HCA127 (Accession NM\_018684). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCA127. HMP19 (Accession XM\_113455) is another VGAM894 host target gene. HMP19 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HMP19, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HMP19 BINDING SITE, designated SEQ ID:42274, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33930] Another function of VGAM894 is therefore inhibition of HMP19 (Accession XM\_113455). Accordingly, utilities of

VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HMP19. ICK (Accession NM\_014920) is another VGAM894 host target gene. ICK BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ICK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ICK BINDING SITE, designated SEQ ID:17198, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33931] Another function of VGAM894 is therefore inhibition of ICK (Accession NM\_014920). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ICK. KIAA0057 (Accession NM\_012288) is another VGAM894 host target gene. KIAA0057 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA0057, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0057 BINDING SITE, designated SEQ ID:14623, to the nucleotide sequence of

VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33932] Another function of VGAM894 is therefore inhibition of KIAA0057 (Accession NM\_012288). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0057. KIAA0319 (Accession NM\_014809) is another VGAM894 host target gene. KIAA0319 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0319, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0319 BINDING SITE, designated SEQ ID:16765, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33933] Another function of VGAM894 is therefore inhibition of KIAA0319 (Accession NM\_014809). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0319. KIAA0354 (Accession NM\_014872) is another VGAM894 host target gene. KIAA0354 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA0354, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0354 BINDING SITE, designated SEQ ID:17000, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33934] Another function of VGAM894 is therefore inhibition of KIAA0354 (Accession NM\_014872). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0354. KIAA0703 (Accession NM\_014861) is another VGAM894 host target gene. KIAA0703 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA0703, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0703 BINDING SITE, designated SEQ ID:16930, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33935] Another function of VGAM894 is therefore inhibition of KIAA0703 (Accession NM\_014861). Accordingly, utilities

of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0703. KIAA0961 (Accession NM\_014898) is another VGAM894 host target gene. KIAA0961 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0961, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0961 BINDING SITE, designated SEQ ID:17074, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33936] Another function of VGAM894 is therefore inhibition of KIAA0961 (Accession NM\_014898). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0961. KIAA1257 (Accession XM\_031577) is another VGAM894 host target gene. KIAA1257 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1257, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of



KIAA1257 BINDING SITE, designated SEQ ID:31442, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33937] Another function of VGAM894 is therefore inhibition of KIAA1257 (Accession XM\_031577). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1257. KIAA1500 (Accession XM\_034353) is another VGAM894 host target gene. KIAA1500 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1500 BINDING SITE, designated SEQ ID:32072, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33938] Another function of VGAM894 is therefore inhibition of KIAA1500 (Accession XM\_034353). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1500. MIC2 Like 1 (MIC2L1, Accession NM\_031462) is another VGAM894 host target gene. MIC2L1 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MIC2L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MIC2L1 BINDING SITE, designated SEQ ID:25493, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33939] Another function of VGAM894 is therefore inhibition of MIC2 Like 1 (MIC2L1, Accession NM\_031462). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MIC2L1. MR (Accession NM\_031212) is another VGAM894 host target gene. MR BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by MR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MR BINDING SITE, designated SEQ ID:25257, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33940] Another function of VGAM894 is therefore inhibition of

MR (Accession NM\_031212). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MR. Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230) is another VGAM894 host target gene. NUDT11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NUDT11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NUDT11 BINDING SITE, designated SEQ ID:30146, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33941] Another function of VGAM894 is therefore inhibition of Nudix (nucleoside diphosphate linked moiety X)-type Motif 11 (NUDT11, Accession XM\_010230). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NUDT11. Protein Phosphatase 2 (formerly 2A), Regulatory Subunit B", Alpha (PPP2R3A, Accession NM\_002718) is another VGAM894 host target gene. PPP2R3A BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by PPP2R3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PPP2R3A BINDING SITE, designated SEQ ID:8587, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33942] Another function of VGAM894 is therefore inhibition of Protein Phosphatase 2 (formerly 2A), Regulatory Subunit B", Alpha (PPP2R3A, Accession NM\_002718). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PPP2R3A. SENP7 (Accession NM\_020654) is another VGAM894 host target gene. SENP7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SENP7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SENP7 BINDING SITE, designated SEQ ID:21823, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33943] Another function of VGAM894 is therefore inhibition of

SENP7 (Accession NM\_020654). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SENP7. Splicing Factor, Arginine/serine-rich 11 (SFRS11, Accession NM\_004768) is another VGAM894 host target gene. SFRS11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRS11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRS11 BINDING SITE, designated SEQ ID:11160, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33944] Another function of VGAM894 is therefore inhibition of Splicing Factor, Arginine/serine-rich 11 (SFRS11, Accession NM\_004768). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRS11. TAF2 RNA Polymerase II, TATA Box Binding Protein (TBP)-associated Factor, 150kDa (TAF2, Accession NM\_003184) is another VGAM894 host target gene. TAF2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by TAF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TAF2 BINDING SITE, designated SEQ ID:9160, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33945] Another function of VGAM894 is therefore inhibition of TAF2 RNA Polymerase II, TATA Box Binding Protein (TBP)-associated Factor, 150kDa (TAF2, Accession NM\_003184). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TAF2. Zinc Metalloprotease (STE24 homolog, yeast) (ZMPSTE24, Accession NM\_005857) is another VGAM894 host target gene. ZMPSTE24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZMPSTE24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZMPSTE24 BINDING SITE, designated SEQ ID:12463, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ

ID:3605.

[33946] Another function of VGAM894 is therefore inhibition of Zinc Metalloproteinase (STE24 homolog, yeast) (ZMPSTE24, Accession NM\_005857). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZMP-STE24. Zinc Finger Protein 262 (ZNF262, Accession NM\_005095) is another VGAM894 host target gene. ZNF262 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF262, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF262 BINDING SITE, designated SEQ ID:11558, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33947] Another function of VGAM894 is therefore inhibition of Zinc Finger Protein 262 (ZNF262, Accession NM\_005095). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF262. LOC147991 (Accession XM\_085993) is another VGAM894 host target gene.

LOC147991 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147991, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147991 BINDING SITE, designated SEQ ID:38438, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33948] Another function of VGAM894 is therefore inhibition of LOC147991 (Accession XM\_085993). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147991. LOC149271 (Accession XM\_086475) is another VGAM894 host target gene. LOC149271 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149271, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149271 BINDING SITE, designated SEQ ID:38682, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.



[33949] Another function of VGAM894 is therefore inhibition of LOC149271 (Accession XM\_086475). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149271. LOC150170 (Accession XM\_086799) is another VGAM894 host target gene. LOC150170 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150170 BINDING SITE, designated SEQ ID:38864, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33950] Another function of VGAM894 is therefore inhibition of LOC150170 (Accession XM\_086799). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150170. LOC150175 (Accession XM\_086806) is another VGAM894 host target gene. LOC150175 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150175, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150175 BINDING SITE, designated SEQ ID:38886, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33951] Another function of VGAM894 is therefore inhibition of LOC150175 (Accession XM\_086806). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150175. LOC150215 (Accession XM\_086813) is another VGAM894 host target gene. LOC150215 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150215, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150215 BINDING SITE, designated SEQ ID:38890, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33952] Another function of VGAM894 is therefore inhibition of LOC150215 (Accession XM\_086813). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC150215. LOC150218 (Accession XM\_086850) is another VGAM894 host target gene. LOC150218 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC150218, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150218 BINDING SITE, designated SEQ ID:38917, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33953] Another function of VGAM894 is therefore inhibition of LOC150218 (Accession XM\_086850). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150218. LOC151201 (Accession XM\_098021) is another VGAM894 host target gene. LOC151201 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151201, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151201 BINDING SITE, designated SEQ ID:41325, to the nucleotide sequence of VGAM894 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3605.

[33954] Another function of VGAM894 is therefore inhibition of LOC151201 (Accession XM\_098021). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151201. LOC206338 (Accession XM\_116456) is another VGAM894 host target gene. LOC206338 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC206338, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC206338 BINDING SITE, designated SEQ ID:43112, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33955] Another function of VGAM894 is therefore inhibition of LOC206338 (Accession XM\_116456). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC206338. LOC221576 (Accession XM\_168088) is another VGAM894 host target gene. LOC221576 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221576, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221576 BINDING SITE, designated SEQ ID:45001, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33956] Another function of VGAM894 is therefore inhibition of LOC221576 (Accession XM\_168088). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221576. LOC257282 (Accession XM\_172844) is another VGAM894 host target gene. LOC257282 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC257282, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257282 BINDING SITE, designated SEQ ID:46123, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33957] Another function of VGAM894 is therefore inhibition of LOC257282 (Accession XM\_172844). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC257282. LOC257515 (Accession XM\_175211) is another VGAM894 host target gene. LOC257515 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257515, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257515 BINDING SITE, designated SEQ ID:46685, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33958] Another function of VGAM894 is therefore inhibition of LOC257515 (Accession XM\_175211). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257515. LOC257572 (Accession XM\_175294) is another VGAM894 host target gene. LOC257572 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257572, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257572 BINDING SITE, designated SEQ ID:46746, to

the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33959] Another function of VGAM894 is therefore inhibition of LOC257572 (Accession XM\_175294). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257572. LOC91445 (Accession XM\_018516) is another VGAM894 host target gene. LOC91445 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC91445, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91445 BINDING SITE, designated SEQ ID:30369, to the nucleotide sequence of VGAM894 RNA, herein designated VGAM RNA, also designated SEQ ID:3605.

[33960] Another function of VGAM894 is therefore inhibition of LOC91445 (Accession XM\_018516). Accordingly, utilities of VGAM894 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91445. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 895 (VGAM895) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[33961] VGAM895 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM895 was detected is described hereinabove with reference to Figs. 1–8.

[33962] VGAM895 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM895 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[33963] VGAM895 gene encodes a VGAM895 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM895 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM895 precursor RNA is designated SEQ ID:881, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:881 is located at position 20248 relative to the genome of Gallid Herpesvirus 2.



[33964] VGAM895 precursor RNA folds onto itself, forming VGAM895 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33965] An enzyme complex designated DICER COMPLEX, `dices` the VGAM895 folded precursor RNA into VGAM895 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM895 RNA is designated SEQ ID:3606, and is provided hereinbelow with reference to the sequence listing part.

[33966] VGAM895 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM895 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM895 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33967] VGAM895 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM895 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM895 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM895 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM895 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33968] The complementary binding of VGAM895 RNA, herein designated VGAM RNA, to host target binding sites on VGAM895 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM895 host target RNA into VGAM895 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33969] It is appreciated that VGAM895 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM895 host target genes. The mRNA of each one of this plurality of VGAM895 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM895 RNA, herein designated VGAM RNA, and which when bound by VGAM895 RNA causes inhibition of translation of respective one or more VGAM895 host target proteins.

[33970] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM895 gene, herein designated VGAM GENE, on one or more VGAM895 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[33971] It is yet further appreciated that a function of VGAM895 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM895 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM895 correlate with, and may be deduced from, the identity of the

host target genes which VGAM895 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33972] Nucleotide sequences of the VGAM895 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM895 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM895 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM895 are further described hereinbelow with reference to Table 1.

[33973] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM895 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM895 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[33974] As mentioned hereinabove with reference to Fig. 1, a function of VGAM895 gene, herein designated VGAM is inhibition of expression of VGAM895 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM895 correlate with, and may be deduced from, the identity of the target genes which VGAM895

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33975] KOC1 (Accession XM\_165847) is a VGAM895 host target gene. KOC1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KOC1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KOC1 BINDING SITE, designated SEQ ID:43781, to the nucleotide sequence of VGAM895 RNA, herein designated VGAM RNA, also designated SEQ ID:3606.

[33976] A function of VGAM895 is therefore inhibition of KOC1 (Accession XM\_165847). Accordingly, utilities of VGAM895 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KOC1. SE57-1 (Accession NM\_025214) is another VGAM895 host target gene. SE57-1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SE57-1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SE57-1 BINDING SITE, designated SEQ ID:24890, to the nucleotide sequence of VGAM895

RNA, herein designated VGAM RNA, also designated SEQ ID:3606.

- [33977] Another function of VGAM895 is therefore inhibition of SE57-1 (Accession NM\_025214). Accordingly, utilities of VGAM895 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SE57-1. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 896 (VGAM896) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.
- [33978] VGAM896 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM896 was detected is described hereinabove with reference to Figs. 1-8.
- [33979] VGAM896 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM896 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.
- [33980] VGAM896 gene encodes a VGAM896 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM896 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM896 precursor RNA is designated SEQ ID:882, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:882 is located at position 21611 relative to the genome of Gallid Herpesvirus 2.

[33981] VGAM896 precursor RNA folds onto itself, forming VGAM896 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[33982] An enzyme complex designated DICER COMPLEX, `dices` the VGAM896 folded precursor RNA into VGAM896 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex



comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM896 RNA is designated SEQ ID:3607, and is provided hereinbelow with reference to the sequence listing part.

[33983] VGAM896 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM896 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM896 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[33984] VGAM896 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM896 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM896 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM896 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM896 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[33985] The complementary binding of VGAM896 RNA, herein designated VGAM RNA, to host target binding sites on VGAM896 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM896 host target RNA into VGAM896 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[33986] It is appreciated that VGAM896 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM896 host target genes. The mRNA of

each one of this plurality of VGAM896 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM896 RNA, herein designated VGAM RNA, and which when bound by VGAM896 RNA causes inhibition of translation of respective one or more VGAM896 host target proteins.

[33987] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM896 gene, herein designated VGAM GENE, on one or more VGAM896 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[33988] It is yet further appreciated that a function of VGAM896 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM896 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM896 correlate with, and may be deduced from, the identity of the host target genes which VGAM896 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[33989] Nucleotide sequences of the VGAM896 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM896 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM896 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM896 are further described hereinbelow with reference to Table 1.

[33990] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM896 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM896 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[33991] As mentioned hereinabove with reference to Fig. 1, a function of VGAM896 gene, herein designated VGAM is inhibition of expression of VGAM896 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM896 correlate with, and may be deduced from, the identity of the target genes which VGAM896 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[33992] B-cell CLL/lymphoma 9 (BCL9, Accession NM\_004326) is a VGAM896 host target gene. BCL9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL9 BINDING SITE, designated SEQ ID:10521, to the nucleotide sequence of VGAM896 RNA, herein designated VGAM RNA, also designated SEQ ID:3607.

[33993] A function of VGAM896 is therefore inhibition of B-cell CLL/lymphoma 9 (BCL9, Accession NM\_004326), a gene which recruits of PYGO to the nuclear beta-catenin-TCF

complex in Wnt/Wingless signaling. Accordingly, utilities of VGAM896 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL9. The function of BCL9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74. Filamin B, Beta (actin binding protein 278) (FLNB, Accession XM\_030806) is another VGAM896 host target gene. FLNB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLNB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLNB BINDING SITE, designated SEQ ID:31137, to the nucleotide sequence of VGAM896 RNA, herein designated VGAM RNA, also designated SEQ ID:3607.

[33994] Another function of VGAM896 is therefore inhibition of Filamin B, Beta (actin binding protein 278) (FLNB, Accession XM\_030806), a gene which Filamin B, beta; binds actin, interacts with cytoplasmic domain of Ibalpha. Accordingly, utilities of VGAM896 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with FLNB. The function of FLNB and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM416. Chromosome 20 Open Reading Frame 103 (C20orf103, Accession NM\_012261) is another VGAM896 host target gene. C20orf103 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf103, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf103 BINDING SITE, designated SEQ ID:14567, to the nucleotide sequence of VGAM896 RNA, herein designated VGAM RNA, also designated SEQ ID:3607.

[33995] Another function of VGAM896 is therefore inhibition of Chromosome 20 Open Reading Frame 103 (C20orf103, Accession NM\_012261). Accordingly, utilities of VGAM896 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf103. Solute Carrier Family 5 (choline transporter), Member 7 (SLC5A7, Accession NM\_021815) is another VGAM896 host target gene. SLC5A7 BINDING SITE is HOST TARGET binding site

found in the 3' untranslated region of mRNA encoded by SLC5A7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC5A7 BINDING SITE, designated SEQ ID:22392, to the nucleotide sequence of VGAM896 RNA, herein designated VGAM RNA, also designated SEQ ID:3607.

[33996] Another function of VGAM896 is therefore inhibition of Solute Carrier Family 5 (choline transporter), Member 7 (SLC5A7, Accession NM\_021815). Accordingly, utilities of VGAM896 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC5A7. LOC197201 (Accession XM\_113839) is another VGAM896 host target gene. LOC197201 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC197201, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC197201 BINDING SITE, designated SEQ ID:42462, to the nucleotide sequence of VGAM896 RNA, herein designated VGAM RNA, also designated SEQ ID:3607.



[33997] Another function of VGAM896 is therefore inhibition of LOC197201 (Accession XM\_113839). Accordingly, utilities of VGAM896 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC197201. LOC254122 (Accession XM\_170660) is another VGAM896 host target gene. LOC254122 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC254122, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC254122 BINDING SITE, designated SEQ ID:45434, to the nucleotide sequence of VGAM896 RNA, herein designated VGAM RNA, also designated SEQ ID:3607.

[33998] Another function of VGAM896 is therefore inhibition of LOC254122 (Accession XM\_170660). Accordingly, utilities of VGAM896 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC254122. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 897 (VGAM897) viral gene, which modulates expression of respective host target genes thereof,

the function and utility of which host target genes is known in the art.

[33999] VGAM897 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM897 was detected is described hereinabove with reference to Figs. 1–8.

[34000] VGAM897 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Gallid Herpesvirus 2. VGAM897 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34001] VGAM897 gene encodes a VGAM897 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM897 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM897 precursor RNA is designated SEQ ID:883, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:883 is located at position 20974 relative to the genome of Gallid Herpesvirus 2.

[34002] VGAM897 precursor RNA folds onto itself, forming VGAM897 folded precursor RNA, herein designated VGAM

FOLDED PRECURSOR RNA, which has a two-dimensional  
`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[34003] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM897 folded precursor RNA into VGAM897 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 59%) nucleotide se-  
quence of VGAM897 RNA is designated SEQ ID:3608, and  
is provided hereinbelow with reference to the sequence  
listing part.

[34004] VGAM897 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM897 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM897 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding

gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34005] VGAM897 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM897 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM897 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM897 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM897 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in

the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34006] The complementary binding of VGAM897 RNA, herein designated VGAM RNA, to host target binding sites on VGAM897 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM897 host target RNA into VGAM897 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34007] It is appreciated that VGAM897 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM897 host target genes. The mRNA of each one of this plurality of VGAM897 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM897 RNA, herein designated VGAM RNA, and which when bound by VGAM897 RNA causes inhibition of translation of respective one or more VGAM897 host target proteins.

[34008] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by

VGAM897 gene, herein designated VGAM GENE, on one or more VGAM897 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34009] It is yet further appreciated that a function of VGAM897 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of viral infection by Gallid Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM897 correlate with, and may be deduced from, the identity of the host target genes which VGAM897 binds and inhibits, and the function of these host target genes, as elaborated

hereinbelow.

[34010] Nucleotide sequences of the VGAM897 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM897 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM897 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM897 are further described hereinbelow with reference to Table 1.

[34011] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM897 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM897 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34012] As mentioned hereinabove with reference to Fig. 1, a function of VGAM897 gene, herein designated VGAM is inhibition of expression of VGAM897 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM897 correlate with, and may be deduced from, the identity of the target genes which VGAM897 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34013] Cytoplasmic Linker Associated Protein 2 (CLASP2, Accession XM\_035453) is a VGAM897 host target gene. CLASP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CLASP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLASP2 BINDING SITE, designated SEQ ID:32269, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34014] A function of VGAM897 is therefore inhibition of Cytoplasmic Linker Associated Protein 2 (CLASP2, Accession XM\_035453), a gene which is involved in the regional regulation of microtubule dynamics in motile fibroblasts. Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLASP2. The function of CLASP2 has been established by previous studies. CLIP170 (OMIM Ref. No. 179838) and CLIP115 (OMIM Ref. No. 603432) are cytoplasmic linker proteins that associate specifically with the ends of growing microtubules and may act as anticrotrophe factors. Using a yeast 2-hybrid screen with an N-terminal region of CLIP115 as bait, followed by cDNA li-



brary screening, RACE analysis, and EST database searching, Akhmanova et al. (2001) identified mouse and human cDNAs encoding 2 CLIP-associated proteins, CLASP1 (OMIM Ref. No. 605852) and CLASP2. The CLASPs are homologous to a *Drosophila* microtubule-associated protein termed Orbit or Mast. CLASP1 is identical to the protein encoded by a partial cDNA, KIAA0622, identified by Ishikawa et al. (1998), although the KIAA0622 protein lacks the N-terminal 249 amino acids of the 1,538-amino acid CLASP1 protein reported by Akhmanova et al. (2001). CLASP2 shares approximately 75% identity with the KIAA0627 protein, which is encoded by a partial cDNA also identified by Ishikawa et al. (1998). There are several CLASP isoforms due to alternative splicing. Northern blot analysis of mouse tissues detected highest expression of Clasp1 in brain, heart, and testis, while Clasp2 mRNAs were enriched in the brain. The Clasp2-beta transcript appeared to be brain specific. By RT-PCR analysis, Ishikawa et al. (1998) detected variable but ubiquitous expression of CLASP2, or KIAA0627, except in spleen. Akhmanova et al. (2001) showed that CLASPs bind CLIPs and microtubules, colocalize with the CLIPs at microtubule distal ends, and have microtubule-stabilizing effects in

transfected cells. After serum induction, CLASPs relocate to distal segments of microtubules at the leading edge of motile fibroblasts. Akhmanova et al. (2001) provided evidence that this asymmetric CLASP distribution is mediated by phosphatidylinositol 3-kinase (see OMIM Ref. No. 171834) and glycogen synthase kinase 3-beta (OMIM Ref. No. 605004). Antibody injections suggested that CLASP2 is required for the orientation of stabilized microtubules toward the leading edge. The authors proposed that CLASPs are involved in the local regulation of microtubule dynamics in response to positional cues.

[34015] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34016] Akhmanova, A.; Hoogenraad, C. C.; Drabek, K.; Stepanova, T.; Dortland, B.; Verkerk, T.; Vermeulen, W.; Burgering, B. M.; De Zeeuw, C. I.; Grosveld, F.; Galjart, N. : CLASPs are CLIP-115 and -170 associating proteins involved in the regional regulation of microtubule dynamics in motile fibroblasts. *Cell* 104: 923-935, 2001. ; and

[34017] Ishikawa, K.; Nagase, T.; Suyama, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. X.

The complete sequ.

[34018] Further studies establishing the function and utilities of CLASP2 are found in John Hopkins OMIM database record ID 605853, and in cited publications numbered 662 and 9440 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fucosyltransferase 1 (galactoside 2-alpha-L-fucosyltransferase, Bombay phenotype included) (FUT1, Accession NM\_000148) is another VGAM897 host target gene. FUT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FUT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FUT1 BINDING SITE, designated SEQ ID:5645, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34019] Another function of VGAM897 is therefore inhibition of Fucosyltransferase 1 (galactoside 2-alpha-L-fucosyltransferase, Bombay phenotype included) (FUT1, Accession NM\_000148). Accordingly, utilities of VGAM897 include diagnosis, prevention and treat-

ment of diseases and clinical conditions associated with FUT1. Nuclear Receptor Subfamily 4, Group A, Member 1 (NR4A1, Accession NM\_002135) is another VGAM897 host target gene. NR4A1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NR4A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NR4A1 BINDING SITE, designated SEQ ID:7911, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34020] Another function of VGAM897 is therefore inhibition of Nuclear Receptor Subfamily 4, Group A, Member 1 (NR4A1, Accession NM\_002135), a gene which is a member of steroid receptor family and binds DNA. Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NR4A1. The function of NR4A1 has been established by previous studies. Ryseck et al. (1989) characterized a growth factor-inducible gene, N10, encoding a nuclear protein of 601 amino acids with similarities to members of the steroid and thyroid hormone receptor families. The

gene is rapidly but transiently induced by several mitogens. The N10 transcription unit is 8 kb long and split into 7 exons. The exon–intron distribution is similar to that of other members of the nuclear receptor superfamily. The gene was assigned to mouse chromosome 15 and human chromosome 12 (12q13) by in situ hybridization. These localizations are close to that of the gene encoding gamma retinoic acid receptor (OMIM Ref. No. 180190). Chang et al. (1989) isolated a member of the steroid receptor superfamily, which they called TR3, from a human prostate cDNA library by use of an oligonucleotide probe to the DNA–binding domain common to members of the steroid receptor superfamily. Sequence analysis of the TR3 cDNA revealed that it encodes a 598–amino acid protein with domains homologous to the DNA–binding and hormone–binding domains of other members of the steroid receptor superfamily. Chang et al. (1989) found that the TR3 receptor shares about 20% amino acid homology with the estrogen receptor and less than 15% homology with other known receptors. The authors noted that the TR3 gene may be the human homolog of the mouse nur77 gene, with which it shares 91% amino acid identity. Expression of the TR3 cDNA in rabbit reticulocyte lysate

produced a 64-kD DNA-binding protein.

[34021] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34022] Chang, C.; Kokontis, J.; Liao, S. S.; Chang, Y. : Isolation and characterization of human TR3 receptor: a member of steroid receptor superfamily. J. Steroid Biochem. 34: 391-395, 1989. ; and

[34023] Ryseck, R.-P.; Macdonald-Bravo, H.; Mattei, M. G.; Siegfried, R. L.; Bravo, R. : Structure, mapping and expression of a growth factor inducible gene encoding a putative nuclear hormonal.

[34024] Further studies establishing the function and utilities of NR4A1 are found in John Hopkins OMIM database record ID 139139, and in cited publications numbered 4728-4737 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Tumor Necrosis Factor Receptor Superfamily, Member 17 (TNFRSF17, Accession NM\_001192) is another VGAM897 host target gene. TNFRSF17 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by TNFRSF17, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFRSF17 BINDING SITE, designated SEQ ID:6862, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34025] Another function of VGAM897 is therefore inhibition of Tumor Necrosis Factor Receptor Superfamily, Member 17 (TNFRSF17, Accession NM\_001192), a gene which associates with B lymphocyte maturation. Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFRSF17. The function of TNFRSF17 has been established by previous studies. Laabi et al. (1992) found that a t(4;16)(q26;p13.1) translocation, found in tumor cells of a patient with intestinal T-cell lymphoma, resulted in a rearrangement of the interleukin-2 gene (IL2; 147680), normally located on 4q26, with sequences from 16p13.1. Use of an IL2-specific probe to screen a cDNA library of tumor cells, Laabi et al. (1992) isolated clones that consisted, from 5-prime to 3-prime, of the 3 first exons of the IL2 gene, followed by a 16p13 in-frame sequence encoding 181 amino acids. A probe derived from this sequence detected a 1.2-kb transcript in various cell lines exhibiting

mature B lymphoid cell features, but this sequence was not detected in other cell lines representative of other hematopoietic lineages, or in other organs. For this reason, the novel gene was termed BCM for B-cell maturation. The open reading frame of normal BCM cDNA predicted a 184-amino acid protein with a single transmembrane domain that had no homology with any protein sequences stored in data banks. Data indicated that the expression of BCM coincides with B-cell terminal maturation. Gras et al. (1995) found that in a myeloma cell line, BCMA is primarily expressed in a perinuclear Golgi-like structure. By transfection of kidney and B-cell lines and flow cytometry and immunofluorescence analysis, Hatzoglou et al. (2000) demonstrated that in addition to the intracytoplasmic localization, BCMA is present on the cell surface. Western blot analysis showed that overexpressed BCMA, like other TNFRs, induces activation of NF $\kappa$ B (OMIM Ref. No. 164011) as well as the MAPK substrate ELK1 (OMIM Ref. No. 311040) and the MAPKs JNK (MAPK8; 601158) and p38 (MAPK14; 600289), but not ERK (OMIM Ref. No. 600997), via its cytoplasmic tail (residues 119 to 143). Cotransfection, immunoprecipitation, and immunoblot analysis indicated that BCMA, again through its cytoplas-



mic tail, associates with TRAF1 601711, TRAF2 601895, and TRAF3 601896, but not with TRAF5 602356, suggesting that these adaptor proteins further propagate signals elicited by TNFRs such as BCMA.

[34026] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34027] Laabi, Y.; Gras, M. P.; Carbonnel, F.; Brouet, J. C.; Berger, R.; Larsen, C. J.; Tsapis, A. : A new gene, BCM, on chromosome 16 is fused to the interleukin 2 gene by a t(4;16)(q26;p13) translocation in a malignant T cell lymphoma. EMBO J. 11: 3897–3904, 1992. ; and

[34028] Hatzoglou, A.; Roussel, J.; Bourgeade, M.–F.; Rogier, E.; Madry, C.; Inoue, J.; Devergne, O.; Tsapis, A. : TNF receptor family member BCMA (B cell maturation) associates with TNF recepto.

[34029] Further studies establishing the function and utilities of TNFRSF17 are found in John Hopkins OMIM database record ID 109545, and in cited publications numbered 50 and 3161 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Chemokine (C–C motif) Receptor 6 (CCR6, Accession NM\_031409) is another VGAM897 host target gene. CCR6

BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CCR6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CCR6 BINDING SITE, designated SEQ ID:25371, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34030] Another function of VGAM897 is therefore inhibition of Chemokine (C-C motif) Receptor 6 (CCR6, Accession NM\_031409). Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CCR6. Down Syndrome Critical Region Gene 1-like 1 (DSCR1L1, Accession NM\_005822) is another VGAM897 host target gene. DSCR1L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DSCR1L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DSCR1L1 BINDING SITE, designated SEQ ID:12430, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ

ID:3608.

[34031] Another function of VGAM897 is therefore inhibition of Down Syndrome Critical Region Gene 1-like 1 (DSCR1L1, Accession NM\_005822). Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSCR1L1.

FLJ10826 (Accession NM\_018233) is another VGAM897 host target gene. FLJ10826 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10826 BINDING SITE, designated SEQ ID:20174, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34032] Another function of VGAM897 is therefore inhibition of FLJ10826 (Accession NM\_018233). Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10826. FLJ12888 (Accession NM\_024945) is another VGAM897 host target gene. FLJ12888 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA

encoded by FLJ12888, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12888 BINDING SITE, designated SEQ ID:24497, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34033] Another function of VGAM897 is therefore inhibition of FLJ12888 (Accession NM\_024945). Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12888. Golgi Phosphoprotein 2 (GOLPH2, Accession NM\_016548) is another VGAM897 host target gene. GOLPH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GOLPH2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GOLPH2 BINDING SITE, designated SEQ ID:18623, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34034] Another function of VGAM897 is therefore inhibition of Golgi Phosphoprotein 2 (GOLPH2, Accession NM\_016548).

Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GOLPH2. LOC168667 (Accession XM\_166592) is another VGAM897 host target gene. LOC168667 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC168667, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC168667 BINDING SITE, designated SEQ ID:44568, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34035] Another function of VGAM897 is therefore inhibition of LOC168667 (Accession XM\_166592). Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC168667. LOC204010 (Accession XM\_115138) is another VGAM897 host target gene. LOC204010 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC204010, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC204010 BINDING SITE, designated SEQ ID:43082, to the nucleotide sequence of VGAM897 RNA, herein designated VGAM RNA, also designated SEQ ID:3608.

[34036] Another function of VGAM897 is therefore inhibition of LOC204010 (Accession XM\_115138). Accordingly, utilities of VGAM897 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC204010. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 898 (VGAM898) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34037] VGAM898 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM898 was detected is described hereinabove with reference to Figs. 1–8.

[34038] VGAM898 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Cowpea Mottle Virus. VGAM898 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the

human genome.

[34039] VGAM898 gene encodes a VGAM898 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM898 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM898 precursor RNA is designated SEQ ID:884, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:884 is located at position 3264 relative to the genome of Cowpea Mottle Virus.

[34040] VGAM898 precursor RNA folds onto itself, forming VGAM898 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34041] An enzyme complex designated DICER COMPLEX, `dices` the VGAM898 folded precursor RNA into VGAM898 RNA, herein designated VGAM RNA, a single stranded ~22 nt

long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 81%) nucleotide sequence of VGAM898 RNA is designated SEQ ID:3609, and is provided hereinbelow with reference to the sequence listing part.

[34042] VGAM898 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM898 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM898 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34043] VGAM898 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM898 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM898 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide se-



quence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM898 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM898 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34044] The complementary binding of VGAM898 RNA, herein designated VGAM RNA, to host target binding sites on VGAM898 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM898 host target RNA into VGAM898 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34045] It is appreciated that VGAM898 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM898 host target genes. The mRNA of each one of this plurality of VGAM898 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM898 RNA, herein designated VGAM RNA, and which when bound by VGAM898 RNA causes inhibition of translation of respective one or more VGAM898 host target proteins.

[34046] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM898 gene, herein designated VGAM GENE, on one or more VGAM898 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, al-

though specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34047] It is yet further appreciated that a function of VGAM898 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM898 include diagnosis, prevention and treatment of viral infection by Cowpea Mottle Virus. Specific functions, and accordingly utilities, of VGAM898 correlate with, and may be deduced from, the identity of the host target genes which VGAM898 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34048] Nucleotide sequences of the VGAM898 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM898 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM898 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM898 are further described hereinbelow with reference to Table 1.

[34049] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of

Fig. 1, found on VGAM898 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM898 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34050] As mentioned hereinabove with reference to Fig. 1, a function of VGAM898 gene, herein designated VGAM is inhibition of expression of VGAM898 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM898 correlate with, and may be deduced from, the identity of the target genes which VGAM898 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34051] DKFZP564O0423 (Accession XM\_166254) is a VGAM898 host target gene. DKFZP564O0423 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP564O0423, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564O0423 BINDING SITE, designated SEQ ID:44069, to the nucleotide sequence of VGAM898 RNA, herein designated VGAM RNA, also designated SEQ ID:3609.

[34052] A function of VGAM898 is therefore inhibition of DKFZP564O0423 (Accession XM\_166254). Accordingly, utilities of VGAM898 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564O0423. FLJ14251 (Accession NM\_024881) is another VGAM898 host target gene. FLJ14251 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14251 BINDING SITE, designated SEQ ID:24322, to the nucleotide sequence of VGAM898 RNA, herein designated VGAM RNA, also designated SEQ ID:3609.

[34053] Another function of VGAM898 is therefore inhibition of FLJ14251 (Accession NM\_024881). Accordingly, utilities of VGAM898 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14251. FLJ32743 (Accession NM\_145020) is another VGAM898 host target gene. FLJ32743 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ32743, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ32743 BINDING SITE, designated SEQ ID:29628, to the nucleotide sequence of VGAM898 RNA, herein designated VGAM RNA, also designated SEQ ID:3609.

[34054] Another function of VGAM898 is therefore inhibition of FLJ32743 (Accession NM\_145020). Accordingly, utilities of VGAM898 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ32743. MGC20486 (Accession NM\_052844) is another VGAM898 host target gene. MGC20486 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC20486, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC20486 BINDING SITE, designated SEQ ID:27423, to the nucleotide sequence of VGAM898 RNA, herein designated VGAM RNA, also designated SEQ ID:3609.

[34055] Another function of VGAM898 is therefore inhibition of MGC20486 (Accession NM\_052844). Accordingly, utilities of VGAM898 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

MGC20486. Zinc Finger Protein 226 (ZNF226, Accession NM\_016444) is another VGAM898 host target gene. ZNF226 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by ZNF226, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF226 BINDING SITE, designated SEQ ID:18564, to the nucleotide sequence of VGAM898 RNA, herein designated VGAM RNA, also designated SEQ ID:3609.

[34056] Another function of VGAM898 is therefore inhibition of Zinc Finger Protein 226 (ZNF226, Accession NM\_016444). Accordingly, utilities of VGAM898 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF226. LOC151614 (Accession XM\_087252) is another VGAM898 host target gene. LOC151614 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC151614, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151614 BINDING SITE, desig-

nated SEQ ID:39141, to the nucleotide sequence of VGAM898 RNA, herein designated VGAM RNA, also designated SEQ ID:3609.

[34057] Another function of VGAM898 is therefore inhibition of LOC151614 (Accession XM\_087252). Accordingly, utilities of VGAM898 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151614. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 899 (VGAM899) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34058] VGAM899 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM899 was detected is described hereinabove with reference to Figs. 1–8.

[34059] VGAM899 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 2. VGAM899 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.



[34060] VGAM899 gene encodes a VGAM899 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM899 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM899 precursor RNA is designated SEQ ID:885, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:885 is located at position 46153 relative to the genome of Human Herpesvirus 2.

[34061] VGAM899 precursor RNA folds onto itself, forming VGAM899 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34062] An enzyme complex designated DICER COMPLEX, `dices` the VGAM899 folded precursor RNA into VGAM899 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 80%) nucleotide sequence of VGAM899 RNA is designated SEQ ID:3610, and is provided hereinbelow with reference to the sequence listing part.

[34063] VGAM899 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM899 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM899 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34064] VGAM899 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM899 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM899 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM899 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM899 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34065] The complementary binding of VGAM899 RNA, herein designated VGAM RNA, to host target binding sites on VGAM899 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM899 host target RNA into VGAM899 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34066] It is appreciated that VGAM899 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM899 host target genes. The mRNA of each one of this plurality of VGAM899 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM899 RNA, herein designated VGAM RNA, and which when bound by VGAM899 RNA causes inhibition of translation of respective one or more VGAM899 host target proteins.

[34067] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM899 gene, herein designated VGAM GENE, on one or more VGAM899 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[34068] It is yet further appreciated that a function of VGAM899 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM899 correlate with, and may be deduced from, the identity of the host target genes which VGAM899 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34069] Nucleotide sequences of the VGAM899 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM899 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM899 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM899 are further described hereinbelow with reference to Table 1.

[34070] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM899 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM899 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34071] As mentioned hereinabove with reference to Fig. 1, a function of VGAM899 gene, herein designated VGAM is inhibition of expression of VGAM899 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM899 correlate with, and may be deduced from, the identity of the target genes which VGAM899 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34072] Aquaporin 6, Kidney Specific (AQP6, Accession NM\_001652) is a VGAM899 host target gene. AQP6 BINDING SITE1 and AQP6 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by AQP6, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AQP6 BINDING SITE1 and AQP6 BINDING SITE2, designated SEQ ID:7358 and SEQ ID:27612 respectively, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ

ID:3610.

[34073] A function of VGAM899 is therefore inhibition of Aquaporin 6, Kidney Specific (AQP6, Accession NM\_001652), a gene which participates in distinct physiologic function such as glomerular filtration, tubular endocytosis, and acid-base metabolism. Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AQP6. The function of AQP6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM340. Calcium Channel, Voltage-dependent, P/Q Type, Alpha 1A Subunit (CACNA1A, Accession NM\_000068) is another VGAM899 host target gene. CACNA1A BINDING SITE1 and CACNA1A BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CACNA1A, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CACNA1A BINDING SITE1 and CACNA1A BINDING SITE2, designated SEQ ID:5515 and SEQ ID:35106 respectively, to the nucleotide sequence of VGAM899 RNA, herein designated

VGAM RNA, also designated SEQ ID:3610.

[34074] Another function of VGAM899 is therefore inhibition of Calcium Channel, Voltage-dependent, P/Q Type, Alpha 1A Subunit (CACNA1A, Accession NM\_000068). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CACNA1A. G Protein-coupled Receptor 62 (GPR62, Accession XM\_116151) is another VGAM899 host target gene. GPR62 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GPR62, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR62 BINDING SITE, designated SEQ ID:43109, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34075] Another function of VGAM899 is therefore inhibition of G Protein-coupled Receptor 62 (GPR62, Accession XM\_116151). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR62. Solute Carrier Family 17 (anion/sugar transporter), Member 5 (SLC17A5, Ac-



cession NM\_012434) is another VGAM899 host target gene. SLC17A5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC17A5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC17A5 BINDING SITE, designated SEQ ID:14812, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34076] Another function of VGAM899 is therefore inhibition of Solute Carrier Family 17 (anion/sugar transporter), Member 5 (SLC17A5, Accession NM\_012434), a gene which is a member of a family of anion/cation symporters. Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC17A5. The function of SLC17A5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM766. Transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase) (TGM2, Accession NM\_004613) is another VGAM899 host target gene. TGM2

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TGM2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TGM2 BINDING SITE, designated SEQ ID:10953, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34077] Another function of VGAM899 is therefore inhibition of Transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase) (TGM2, Accession NM\_004613), a gene which catalyzes the cross-linking of proteins and the conjugation of polyamines to proteins. Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TGM2. The function of TGM2 has been established by previous studies. Transglutaminases (EC 2.3.2.13) are a family of enzymes that catalyze the crosslinking of proteins by epsilon-gamma glutamyl lysine isopeptide bonds. The transglutaminases include factor XIII (plasma transglutaminase; 134570), keratinocyte transglutaminase (TGM1; 190195), hair follicle transglutaminase, prostate transglutaminase (TGM4; 600585), and

tissue transglutaminase (TGM2). Although the overall primary structures of these enzymes appear to be quite different, they all share a common amino acid sequence at the active site (Y-G-Q-C-W) and a strict calcium dependence for their activity. The differences in the primary structures of these different transglutaminases are probably responsible for the diverse biologic functions that they play in physiologic processes such as blood coagulation, epidermal differentiation, seminal fluid coagulation and fertilization, cell differentiation, and apoptosis. Dieterich et al. (1997) demonstrated that tissue transglutaminase is the autoantigen involved in celiac disease (OMIM Ref. No. 212750). Gentile et al. (1991) isolated mouse and human cDNAs encoding tissue transglutaminase. The predicted 687-amino acid human protein is 84% and 81% identical to mouse and guinea pig tissue transglutaminase, respectively. In vitro translated human tissue transglutaminase has an apparent molecular mass of 85 kD by SDS-PAGE. The translated product exhibited calcium-dependent catalytic activity. Northern blot analysis revealed that tissue transglutaminase is expressed as a 3.6-kb mRNA in human endothelial cells. Lu et al. (1995) cloned the promoter region of TGM2, ligated it to a reporter construct,

and demonstrated its activity in transient transfection experiments.

[34078] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34079] Dieterich, W.; Ehnis, T.; Bauer, M.; Donner, P.; Volta, U.; Riecken, E. O.; Schuppan, D. : Identification of tissue transglutaminase as the autoantigen of celiac disease. *Nature Med.* 3: 797–801, 1997. ; and

[34080] Gentile, V.; Saydak, M.; Chiocca, E. A.; Akande, O.; Birckbichler, P. J.; Lee, K. N.; Stein, J. P.; Davies, P. J. A. : Isolation and characterization of cDNA clones to mouse macrophage a.

[34081] Further studies establishing the function and utilities of TGM2 are found in John Hopkins OMIM database record ID 190196, and in cited publications numbered 5736–5740 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Zinc Finger Protein 36, C3H Type-like 1 (ZFP36L1, Accession NM\_004926) is another VGAM899 host target gene. ZFP36L1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ZFP36L1, corresponding to a HOST TARGET binding site such as BINDING

SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFP36L1 BINDING SITE, designated SEQ ID:11363, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34082] Another function of VGAM899 is therefore inhibition of Zinc Finger Protein 36, C3H Type-like 1 (ZFP36L1, Accession NM\_004926), a gene which is a regulatory protein involved in regulating the response to growth factors. Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFP36L1. The function of ZFP36L1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74.ARP1 Actin-related Protein 1 Homolog A, Centractin Alpha (yeast) (ACTR1A, Accession XM\_031949) is another VGAM899 host target gene. ACTR1A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ACTR1A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ACTR1A BINDING SITE,

designated SEQ ID:31532, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34083] Another function of VGAM899 is therefore inhibition of ARP1 Actin-related Protein 1 Homolog A, Centractin Alpha (yeast) (ACTR1A, Accession XM\_031949). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ACTR1A. Chromosome 20 Open Reading Frame 28 (C20orf28, Accession NM\_015417) is another VGAM899 host target gene. C20orf28 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf28, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf28 BINDING SITE, designated SEQ ID:17719, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34084] Another function of VGAM899 is therefore inhibition of Chromosome 20 Open Reading Frame 28 (C20orf28, Accession NM\_015417). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with C20orf28.

KIAA1322 (Accession XM\_052626) is another VGAM899 host target gene. KIAA1322 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1322, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1322 BINDING SITE, designated SEQ ID:36022, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34085] Another function of VGAM899 is therefore inhibition of KIAA1322 (Accession XM\_052626). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1322. KIAA1372 (Accession XM\_166244) is another VGAM899 host target gene. KIAA1372 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1372, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1372 BINDING SITE, designated SEQ ID:44057, to the

nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34086] Another function of VGAM899 is therefore inhibition of KIAA1372 (Accession XM\_166244). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1372. KIAA1453 (Accession NM\_025090) is another VGAM899 host target gene. KIAA1453 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1453, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1453 BINDING SITE, designated SEQ ID:24712, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34087] Another function of VGAM899 is therefore inhibition of KIAA1453 (Accession NM\_025090). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1453. MGC4342 (Accession NM\_024329) is another VGAM899 host target gene. MGC4342 BINDING SITE is HOST TARGET binding site found in the 3' untranslated



region of mRNA encoded by MGC4342, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC4342 BINDING SITE, designated SEQ ID:23622, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34088] Another function of VGAM899 is therefore inhibition of MGC4342 (Accession NM\_024329). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC4342. MICAL (Accession NM\_022765) is another VGAM899 host target gene. MICAL BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MICAL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MICAL BINDING SITE, designated SEQ ID:23010, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34089] Another function of VGAM899 is therefore inhibition of MICAL (Accession NM\_022765). Accordingly, utilities of

VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MICAL. MSTP032 (Accession NM\_025226) is another VGAM899 host target gene. MSTP032 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MSTP032, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MSTP032 BINDING SITE, designated SEQ ID:24907, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34090] Another function of VGAM899 is therefore inhibition of MSTP032 (Accession NM\_025226). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MSTP032. Phosphatidylinositol-4-phosphate 5-kinase, Type I, Gamma (PIP5K1C, Accession XM\_047620) is another VGAM899 host target gene. PIP5K1C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIP5K1C, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the com-

plementarity of the nucleotide sequences of PIP5K1C BINDING SITE, designated SEQ ID:35017, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34091] Another function of VGAM899 is therefore inhibition of Phosphatidylinositol-4-phosphate 5-kinase, Type I, Gamma (PIP5K1C, Accession XM\_047620). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIP5K1C. Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654) is another VGAM899 host target gene. SDC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDC3 BINDING SITE, designated SEQ ID:16082, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34092] Another function of VGAM899 is therefore inhibition of Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with SDC3. Torsin Family 2, Member A (TOR2A, Accession NM\_130459) is another VGAM899 host target gene. TOR2A BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TOR2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TOR2A BINDING SITE, designated SEQ ID:28219, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34093] Another function of VGAM899 is therefore inhibition of Torsin Family 2, Member A (TOR2A, Accession NM\_130459). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TOR2A. LOC125268 (Accession XM\_071960) is another VGAM899 host target gene. LOC125268 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC125268, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC125268 BINDING SITE, desig-

nated SEQ ID:37450, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34094] Another function of VGAM899 is therefore inhibition of LOC125268 (Accession XM\_071960). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC125268. LOC145757 (Accession XM\_085227) is another VGAM899 host target gene. LOC145757 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC145757, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145757 BINDING SITE, designated SEQ ID:37972, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34095] Another function of VGAM899 is therefore inhibition of LOC145757 (Accession XM\_085227). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145757. LOC148397 (Accession XM\_086171) is another VGAM899 host target gene. LOC148397 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC148397, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148397 BINDING SITE, designated SEQ ID:38527, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34096] Another function of VGAM899 is therefore inhibition of LOC148397 (Accession XM\_086171). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148397. LOC148479 (Accession XM\_086204) is another VGAM899 host target gene. LOC148479 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC148479, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148479 BINDING SITE, designated SEQ ID:38539, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34097] Another function of VGAM899 is therefore inhibition of

LOC148479 (Accession XM\_086204). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148479. LOC151568 (Accession NM\_138483) is another VGAM899 host target gene. LOC151568 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151568, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151568 BINDING SITE, designated SEQ ID:28835, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34098] Another function of VGAM899 is therefore inhibition of LOC151568 (Accession NM\_138483). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151568. LOC152633 (Accession XM\_098248) is another VGAM899 host target gene. LOC152633 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC152633, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC152633 BINDING SITE, designated SEQ ID:41532, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34099] Another function of VGAM899 is therefore inhibition of LOC152633 (Accession XM\_098248). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152633. LOC222057 (Accession XM\_166594) is another VGAM899 host target gene. LOC222057 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222057, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222057 BINDING SITE, designated SEQ ID:44572, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34100] Another function of VGAM899 is therefore inhibition of LOC222057 (Accession XM\_166594). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222057. LOC51112 (Accession NM\_016030) is an-



other VGAM899 host target gene. LOC51112 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51112, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51112 BINDING SITE, designated SEQ ID:18112, to the nucleotide sequence of VGAM899 RNA, herein designated VGAM RNA, also designated SEQ ID:3610.

[34101] Another function of VGAM899 is therefore inhibition of LOC51112 (Accession NM\_016030). Accordingly, utilities of VGAM899 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51112. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 900 (VGAM900) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34102] VGAM900 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM900 was detected is described

hereinabove with reference to Figs. 1–8.

[34103] VGAM900 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 5. VGAM900 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34104] VGAM900 gene encodes a VGAM900 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM900 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM900 precursor RNA is designated SEQ ID:886, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:886 is located at position 111776 relative to the genome of Human Herpesvirus 5.

[34105] VGAM900 precursor RNA folds onto itself, forming VGAM900 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34106] An enzyme complex designated DICER COMPLEX, `dices` the VGAM900 folded precursor RNA into VGAM900 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 82%) nucleotide sequence of VGAM900 RNA is designated SEQ ID:3611, and is provided hereinbelow with reference to the sequence listing part.

[34107] VGAM900 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM900 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM900 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34108] VGAM900 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM900 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM900 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM900 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM900 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34109] The complementary binding of VGAM900 RNA, herein designated VGAM RNA, to host target binding sites on VGAM900 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM900 host target RNA into VGAM900 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34110] It is appreciated that VGAM900 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM900 host target genes. The mRNA of each one of this plurality of VGAM900 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM900 RNA, herein designated VGAM RNA, and which when bound by VGAM900 RNA causes inhibition of translation of respective one or more VGAM900 host target proteins.

[34111] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM900 gene, herein designated VGAM GENE, on one or more VGAM900 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34112] It is yet further appreciated that a function of VGAM900 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 5. Specific functions, and accordingly utilities, of VGAM900 correlate with, and may be deduced from, the identity of the host target genes which VGAM900 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34113] Nucleotide sequences of the VGAM900 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM900 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding

of VGAM900 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM900 are further described hereinbelow with reference to Table 1.

[34114] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM900 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM900 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34115] As mentioned hereinabove with reference to Fig. 1, a function of VGAM900 gene, herein designated VGAM is inhibition of expression of VGAM900 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM900 correlate with, and may be deduced from, the identity of the target genes which VGAM900 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34116] Axin 1 (AXIN1, Accession XM\_027520) is a VGAM900 host target gene. AXIN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AXIN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of AXIN1 BINDING SITE, designated SEQ ID:30511, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34117] A function of VGAM900 is therefore inhibition of Axin 1 (AXIN1, Accession XM\_027520). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AXIN1. CDP-diacylglycerol Synthase (phosphatidate cytidylyl-transferase) 2 (CDS2, Accession NM\_003818) is another VGAM900 host target gene. CDS2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CDS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDS2 BINDING SITE, designated SEQ ID:9909, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34118] Another function of VGAM900 is therefore inhibition of CDP-diacylglycerol Synthase (phosphatidate cytidylyl-transferase) 2 (CDS2, Accession NM\_003818), a gene



which is a key regulator of the amount of PIP2 available for signaling. Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDS2. The function of CDS2 has been established by previous studies.

4,5-bisphosphate (PIP2) plays a central role in *Drosophila* phototransduction. A photoreceptor-specific form of the enzyme CDP-diacylglycerol synthase (CDS; EC 2.7.7.41), which catalyzes the formation of CDP-diacylglycerol from phosphatidic acid, is a key regulator of the amount of PIP2 available for signaling. By screening EST databases, Halford et al. (1998) identified a partial human cDNA with sequence similarity to CDS1 (OMIM Ref. No. 603548). The deduced partial polypeptide, which they designated CDS2, is 69% identical to CDS1. Volta et al. (1999) isolated additional cDNAs encoding mouse and human CDS2. The predicted human CDS2 protein contains 445 amino acids with 9 transmembrane domains. The sequences of human CDS2 and *Drosophila* CDS proteins are 65% identical. Northern blot analysis revealed that CDS2 was expressed as greater than 9.5-, 4.4-, and approximately 3-kb mRNAs in all tissues tested. In situ hybridization to adult and embryonic mouse tissue sections showed that *Cds2* is

highly expressed in the differentiating neuroblasts of the neural retina and in the central nervous system during embryonic development, although not in the adult retina.

[34119] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34120] Halford, S.; Dulai, K. S.; Daw, S. C.; Fitzgibbon, J.; Hunt, D. M. : Isolation and chromosomal localization of two human CDP-diacylglycerol synthase (CDS) genes. Genomics 54: 140–144, 1998. ; and

[34121] Volta, M.; Bulfone, A.; Gattuso, C.; Rossi, E.; Mariani, M.; Consalez, G. G.; Zuffardi, O.; Ballabio, A.; Banfi, S.; Franco, B. : Identification and characterization of CDS2, a mammalia.

[34122] Further studies establishing the function and utilities of CDS2 are found in John Hopkins OMIM database record ID 603549, and in cited publications numbered 4946–4947 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Kinesin Family Member 3C (KIF3C, Accession NM\_002254) is another VGAM900 host target gene. KIF3C BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIF3C, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIF3C BINDING SITE, designated SEQ ID:8057, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34123] Another function of VGAM900 is therefore inhibition of Kinesin Family Member 3C (KIF3C, Accession NM\_002254). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIF3C. Lymphoblastic Leukemia Derived Sequence 1 (LYL1, Accession NM\_005583) is another VGAM900 host target gene. LYL1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LYL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LYL1 BINDING SITE, designated SEQ ID:12109, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34124] Another function of VGAM900 is therefore inhibition of Lymphoblastic Leukemia Derived Sequence 1 (LYL1, Ac-

cession NM\_005583), a gene which has a Putative helix-loop-helix DNA binding factor;. Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LYL1. The function of LYL1 has been established by previous studies. suggested that LYAAT1 is a lysosomal transporter that actively exports neutral amino acids from lysosomes by chemiosmotic coupling to the H(+)-ATPase of these organelles.

[34125] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34126] Kuo, S. S.; Mellentin, J. D.; Copeland, N. G.; Gilbert, D. J.; Jenkins, N. A.; Cleary, M. L. : Structure, chromosome mapping, and expression of the mouse Lyl-1 gene. *Oncogene* 6: 961-968, 1991. ; and

[34127] Trask, B.; Fertitta, A.; Christensen, M.; Youngblom, J.; Bergmann, A.; Copeland, A.; de Jong, P.; Mohrenweiser, H.; Olsen, A.; Carrano, A.; Tynan, K. : Fluorescence in situ hybridization.

[34128] Further studies establishing the function and utilities of LYL1 are found in John Hopkins OMIM database record ID 151440, and in cited publications numbered 3559-356

and 4710 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Retinitis Pigmentosa 2 (X-linked recessive) (RP2, Accession NM\_006915) is another VGAM900 host target gene. RP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RP2 BINDING SITE, designated SEQ ID:13793, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34129] Another function of VGAM900 is therefore inhibition of Retinitis Pigmentosa 2 (X-linked recessive) (RP2, Accession NM\_006915). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RP2. ATP6V1EL2 (Accession NM\_080653) is another VGAM900 host target gene. ATP6V1EL2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ATP6V1EL2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nu-

cleotide sequences of ATP6V1EL2 BINDING SITE, designated SEQ ID:27940, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34130] Another function of VGAM900 is therefore inhibition of ATP6V1EL2 (Accession NM\_080653). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP6V1EL2. Chromosome 20 Open Reading Frame 162 (C20orf162, Accession NM\_080603) is another VGAM900 host target gene. C20orf162 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C20orf162, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf162 BINDING SITE, designated SEQ ID:27916, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34131] Another function of VGAM900 is therefore inhibition of Chromosome 20 Open Reading Frame 162 (C20orf162, Accession NM\_080603). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with C20orf162. GAPCENA (Accession NM\_012197) is another VGAM900 host target gene. GAPCENA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GAPCENA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GAPCENA BINDING SITE, designated SEQ ID:14494, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34132] Another function of VGAM900 is therefore inhibition of GAPCENA (Accession NM\_012197). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GAPCENA. KIAA1126 (Accession XM\_050325) is another VGAM900 host target gene. KIAA1126 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1126, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1126 BINDING SITE, designated SEQ ID:35609, to the nucleotide sequence of

VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34133] Another function of VGAM900 is therefore inhibition of KIAA1126 (Accession XM\_050325). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1126. MGC2574 (Accession NM\_024098) is another VGAM900 host target gene. MGC2574 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC2574, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC2574 BINDING SITE, designated SEQ ID:23538, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34134] Another function of VGAM900 is therefore inhibition of MGC2574 (Accession NM\_024098). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC2574. Ring Finger Protein 24 (RNF24, Accession NM\_007219) is another VGAM900 host target gene. RNF24 BINDING SITE is HOST TARGET binding site found



in the 5' untranslated region of mRNA encoded by RNF24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNF24 BINDING SITE, designated SEQ ID:14086, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34135] Another function of VGAM900 is therefore inhibition of Ring Finger Protein 24 (RNF24, Accession NM\_007219). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNF24. Rpo1-2 (Accession NM\_032212) is another VGAM900 host target gene. Rpo1-2 BINDING SITE1 and Rpo1-2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by Rpo1-2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of Rpo1-2 BINDING SITE1 and Rpo1-2 BINDING SITE2, designated SEQ ID:25931 and SEQ ID:21096 respectively, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ

ID:3611.

[34136] Another function of VGAM900 is therefore inhibition of Rpo1-2 (Accession NM\_032212). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with Rpo1-2. LOC221416 (Accession XM\_168094) is another VGAM900 host target gene. LOC221416 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221416, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221416 BINDING SITE, designated SEQ ID:45025, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34137] Another function of VGAM900 is therefore inhibition of LOC221416 (Accession XM\_168094). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221416. LOC253502 (Accession XM\_170561) is another VGAM900 host target gene. LOC253502 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC253502, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253502 BINDING SITE, designated SEQ ID:45382, to the nucleotide sequence of VGAM900 RNA, herein designated VGAM RNA, also designated SEQ ID:3611.

[34138] Another function of VGAM900 is therefore inhibition of LOC253502 (Accession XM\_170561). Accordingly, utilities of VGAM900 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253502. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 901 (VGAM901) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34139] VGAM901 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM901 was detected is described hereinabove with reference to Figs. 1–8.

[34140] VGAM901 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Sulfolobus Virus SIRV–1.

VGAM901 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34141] VGAM901 gene encodes a VGAM901 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM901 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM901 precursor RNA is designated SEQ ID:887, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:887 is located at position 8223 relative to the genome of Sulfolobus Virus SIRV-1.

[34142] VGAM901 precursor RNA folds onto itself, forming VGAM901 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34143] An enzyme complex designated DICER COMPLEX, `dices`

the VGAM901 folded precursor RNA into VGAM901 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide sequence of VGAM901 RNA is designated SEQ ID:3612, and is provided hereinbelow with reference to the sequence listing part.

[34144] VGAM901 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM901 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM901 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34145] VGAM901 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM901 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nu-

cleotide sequence of VGAM901 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM901 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM901 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34146] The complementary binding of VGAM901 RNA, herein designated VGAM RNA, to host target binding sites on VGAM901 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM901 host target RNA into VGAM901 host target protein, herein desig-

nated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34147] It is appreciated that VGAM901 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM901 host target genes. The mRNA of each one of this plurality of VGAM901 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM901 RNA, herein designated VGAM RNA, and which when bound by VGAM901 RNA causes inhibition of translation of respective one or more VGAM901 host target proteins.

[34148] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM901 gene, herein designated VGAM GENE, on one or more VGAM901 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are

also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34149] It is yet further appreciated that a function of VGAM901 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM901 include diagnosis, prevention and treatment of viral infection by Sulfolobus Virus SIRV-1. Specific functions, and accordingly utilities, of VGAM901 correlate with, and may be deduced from, the identity of the host target genes which VGAM901 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34150] Nucleotide sequences of the VGAM901 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM901 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM901 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM901 are further described hereinbelow with reference to Table 1.



- [34151] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM901 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM901 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [34152] As mentioned hereinabove with reference to Fig. 1, a function of VGAM901 gene, herein designated VGAM is inhibition of expression of VGAM901 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM901 correlate with, and may be deduced from, the identity of the target genes which VGAM901 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [34153] Centaurin, Delta 1 (CENTD1, Accession NM\_139182) is a VGAM901 host target gene. CENTD1 BINDING SITE1 and CENTD1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by CENTD1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CENTD1 BINDING SITE1 and CENTD1 BIND-

ING SITE2, designated SEQ ID:29200 and SEQ ID:17562 respectively, to the nucleotide sequence of VGAM901 RNA, herein designated VGAM RNA, also designated SEQ ID:3612.

[34154] A function of VGAM901 is therefore inhibition of Centaurin, Delta 1 (CENTD1, Accession NM\_139182), a gene which is involved in cell signaling/communication. Accordingly, utilities of VGAM901 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CENTD1. The function of CENTD1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM445.TEM5 (Accession NM\_032777) is another VGAM901 host target gene. TEM5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TEM5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TEM5 BINDING SITE, designated SEQ ID:26521, to the nucleotide sequence of VGAM901 RNA, herein designated VGAM RNA, also designated SEQ ID:3612.

[34155] Another function of VGAM901 is therefore inhibition of

TEM5 (Accession NM\_032777), a gene which involves in development of midline glia and commissural axon pathways. Accordingly, utilities of VGAM901 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TEM5. The function of TEM5 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM406. EFA6R (Accession NM\_015310) is another VGAM901 host target gene. EFA6R BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by EFA6R, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EFA6R BINDING SITE, designated SEQ ID:17627, to the nucleotide sequence of VGAM901 RNA, herein designated VGAM RNA, also designated SEQ ID:3612.

[34156] Another function of VGAM901 is therefore inhibition of EFA6R (Accession NM\_015310). Accordingly, utilities of VGAM901 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EFA6R. FLJ13910 (Accession NM\_022780) is another VGAM901 host target gene. FLJ13910 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ13910, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13910 BINDING SITE, designated SEQ ID:23059, to the nucleotide sequence of VGAM901 RNA, herein designated VGAM RNA, also designated SEQ ID:3612.

[34157] Another function of VGAM901 is therefore inhibition of FLJ13910 (Accession NM\_022780). Accordingly, utilities of VGAM901 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13910. KIAA1077 (Accession XM\_053496) is another VGAM901 host target gene. KIAA1077 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1077, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1077 BINDING SITE, designated SEQ ID:36094, to the nucleotide sequence of VGAM901 RNA, herein designated VGAM RNA, also designated SEQ ID:3612.

[34158] Another function of VGAM901 is therefore inhibition of

KIAA1077 (Accession XM\_053496). Accordingly, utilities of VGAM901 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1077. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 902 (VGAM902) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34159] VGAM902 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM902 was detected is described hereinabove with reference to Figs. 1–8.

[34160] VGAM902 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Sulfolobus Virus SIRV–1. VGAM902 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34161] VGAM902 gene encodes a VGAM902 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM902 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM902 precursor RNA is designated SEQ ID:888, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:888 is located at position 8730 relative to the genome of Sulfolobus Virus SIRV-1.

[34162] VGAM902 precursor RNA folds onto itself, forming VGAM902 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34163] An enzyme complex designated DICER COMPLEX, `dices` the VGAM902 folded precursor RNA into VGAM902 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide se-

quence of VGAM902 RNA is designated SEQ ID:3613, and is provided hereinbelow with reference to the sequence listing part.

[34164] VGAM902 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM902 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM902 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34165] VGAM902 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM902 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM902 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM902 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM902 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[34166] The complementary binding of VGAM902 RNA, herein designated VGAM RNA, to host target binding sites on VGAM902 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM902 host target RNA into VGAM902 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34167] It is appreciated that VGAM902 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM902 host target genes. The mRNA of each one of this plurality of VGAM902 host target genes comprises one or more host target binding sites, each



having a nucleotide sequence which is at least partly complementary to VGAM902 RNA, herein designated VGAM RNA, and which when bound by VGAM902 RNA causes inhibition of translation of respective one or more VGAM902 host target proteins.

[34168] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM902 gene, herein designated VGAM GENE, on one or more VGAM902 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34169] It is yet further appreciated that a function of VGAM902 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM902 include diagnosis, prevention and treatment of viral infection by Sulfolobus Virus SIRV-1. Specific functions, and accordingly utilities, of VGAM902 correlate with, and may be deduced from, the identity of the host target genes which VGAM902 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34170] Nucleotide sequences of the VGAM902 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM902 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM902 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM902 are further described hereinbelow with reference to Table 1.

[34171] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM902 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM902 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34172] As mentioned hereinabove with reference to Fig. 1, a function of VGAM902 gene, herein designated VGAM is inhibition of expression of VGAM902 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM902 correlate with, and may be deduced from, the identity of the target genes which VGAM902 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34173] Histone Deacetylase 4 (HDAC4, Accession NM\_006037) is a VGAM902 host target gene. HDAC4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HDAC4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HDAC4 BINDING SITE, designated SEQ ID:12659, to the nucleotide sequence of VGAM902 RNA, herein designated VGAM RNA, also designated SEQ ID:3613.

[34174] A function of VGAM902 is therefore inhibition of Histone Deacetylase 4 (HDAC4, Accession NM\_006037), a gene which is responsible for the deacetylation of lysine residues on the n-terminal part of the core histones and may mediate transcriptional regulation. Accordingly, utili-

ties of VGAM902 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HDAC4. The function of HDAC4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM264. Ubiquitin-conjugating Enzyme E2A (RAD6 homolog) (UBE2A, Accession NM\_003336) is another VGAM902 host target gene. UBE2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UBE2A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBE2A BINDING SITE, designated SEQ ID:9339, to the nucleotide sequence of VGAM902 RNA, herein designated VGAM RNA, also designated SEQ ID:3613.

[34175] Another function of VGAM902 is therefore inhibition of Ubiquitin-conjugating Enzyme E2A (RAD6 homolog) (UBE2A, Accession NM\_003336), a gene which catalyzes the covalent attachment of ubiquitin to other proteins and is required for postreplication repair of uv-damaged dna. Accordingly, utilities of VGAM902 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with UBE2A. The function of UBE2A and its association with various diseases and clinical conditions, has been established by previous studies, as described herein above with reference to VGAM294. Chromosome 20 Open Reading Frame 54 (C20orf54, Accession NM\_033409) is another VGAM902 host target gene. C20orf54 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C20orf54, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf54 BINDING SITE, designated SEQ ID:27226, to the nucleotide sequence of VGAM902 RNA, herein designated VGAM RNA, also designated SEQ ID:3613.

[34176] Another function of VGAM902 is therefore inhibition of Chromosome 20 Open Reading Frame 54 (C20orf54, Accession NM\_033409). Accordingly, utilities of VGAM902 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf54. CAP350 (Accession NM\_014810) is another VGAM902 host target gene. CAP350 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

CAP350, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CAP350 BINDING SITE, designated SEQ ID:16770, to the nucleotide sequence of VGAM902 RNA, herein designated VGAM RNA, also designated SEQ ID:3613.

[34177] Another function of VGAM902 is therefore inhibition of CAP350 (Accession NM\_014810). Accordingly, utilities of VGAM902 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CAP350. Phytoceramidase, Alkaline (PHCA, Accession NM\_018367) is another VGAM902 host target gene. PHCA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PHCA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PHCA BINDING SITE, designated SEQ ID:20374, to the nucleotide sequence of VGAM902 RNA, herein designated VGAM RNA, also designated SEQ ID:3613.

[34178] Another function of VGAM902 is therefore inhibition of Phytoceramidase, Alkaline (PHCA, Accession NM\_018367).

Accordingly, utilities of VGAM902 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PHCA. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 903 (VGAM903) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34179] VGAM903 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM903 was detected is described hereinabove with reference to Figs. 1–8.

[34180] VGAM903 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Melanoplus Sanguinipes Entomopoxvirus. VGAM903 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34181] VGAM903 gene encodes a VGAM903 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM903 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide se–

quence of VGAM903 precursor RNA is designated SEQ ID:889, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:889 is located at position 178832 relative to the genome of Melanoplus Sanguinipes Entomopoxvirus.

[34182] VGAM903 precursor RNA folds onto itself, forming VGAM903 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34183] An enzyme complex designated DICER COMPLEX, `dices` the VGAM903 folded precursor RNA into VGAM903 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 84%) nucleotide sequence of VGAM903 RNA is designated SEQ ID:3614, and



is provided hereinbelow with reference to the sequence listing part.

[34184] VGAM903 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM903 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM903 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34185] VGAM903 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM903 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM903 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limit-

ing – VGAM903 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM903 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34186] The complementary binding of VGAM903 RNA, herein designated VGAM RNA, to host target binding sites on VGAM903 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM903 host target RNA into VGAM903 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34187] It is appreciated that VGAM903 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM903 host target genes. The mRNA of each one of this plurality of VGAM903 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly com-

plementary to VGAM903 RNA, herein designated VGAM RNA, and which when bound by VGAM903 RNA causes inhibition of translation of respective one or more VGAM903 host target proteins.

[34188] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM903 gene, herein designated VGAM GENE, on one or more VGAM903 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34189] It is yet further appreciated that a function of VGAM903 is inhibition of expression of host target genes, as part of a

novel viral mechanism of attacking a host. Accordingly, utilities of VGAM903 include diagnosis, prevention and treatment of viral infection by Melanoplus Sanguinipes Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM903 correlate with, and may be deduced from, the identity of the host target genes which VGAM903 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34190] Nucleotide sequences of the VGAM903 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM903 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM903 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM903 are further described hereinbelow with reference to Table 1.

[34191] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM903 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM903 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34192] As mentioned hereinabove with reference to Fig. 1, a

function of VGAM903 gene, herein designated VGAM is inhibition of expression of VGAM903 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM903 correlate with, and may be deduced from, the identity of the target genes which VGAM903 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34193] FLJ20707 (Accession NM\_017936) is a VGAM903 host target gene. FLJ20707 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20707, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20707 BINDING SITE, designated SEQ ID:19628, to the nucleotide sequence of VGAM903 RNA, herein designated VGAM RNA, also designated SEQ ID:3614.

[34194] A function of VGAM903 is therefore inhibition of FLJ20707 (Accession NM\_017936). Accordingly, utilities of VGAM903 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20707. FLJ21934 (Accession NM\_024743) is another VGAM903 host target gene. FLJ21934 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ21934, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21934 BINDING SITE, designated SEQ ID:24080, to the nucleotide sequence of VGAM903 RNA, herein designated VGAM RNA, also designated SEQ ID:3614.

[34195] Another function of VGAM903 is therefore inhibition of FLJ21934 (Accession NM\_024743). Accordingly, utilities of VGAM903 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21934. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 904 (VGAM904) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34196] VGAM904 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM904 was detected is described hereinabove with reference to Figs. 1-8.

[34197] VGAM904 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Melanoplus Sanguinipes Entomopoxvirus. VGAM904 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34198] VGAM904 gene encodes a VGAM904 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM904 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM904 precursor RNA is designated SEQ ID:890, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:890 is located at position 179537 relative to the genome of Melanoplus Sanguinipes Entomopoxvirus.

[34199] VGAM904 precursor RNA folds onto itself, forming VGAM904 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34200] An enzyme complex designated DICER COMPLEX, `dices` the VGAM904 folded precursor RNA into VGAM904 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 49%) nucleotide sequence of VGAM904 RNA is designated SEQ ID:3615, and is provided hereinbelow with reference to the sequence listing part.

[34201] VGAM904 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM904 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM904 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34202] VGAM904 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM904 host target RNA, herein designated VGAM HOST TARGET RNA. This



complementary binding is due to the fact that the nucleotide sequence of VGAM904 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM904 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM904 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34203] The complementary binding of VGAM904 RNA, herein designated VGAM RNA, to host target binding sites on VGAM904 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM904 host tar-

get RNA into VGAM904 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34204] It is appreciated that VGAM904 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM904 host target genes. The mRNA of each one of this plurality of VGAM904 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM904 RNA, herein designated VGAM RNA, and which when bound by VGAM904 RNA causes inhibition of translation of respective one or more VGAM904 host target proteins.

[34205] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM904 gene, herein designated VGAM GENE, on one or more VGAM904 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34206] It is yet further appreciated that a function of VGAM904 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM904 include diagnosis, prevention and treatment of viral infection by Melanoplus Sanguinipes Entomopoxvirus. Specific functions, and accordingly utilities, of VGAM904 correlate with, and may be deduced from, the identity of the host target genes which VGAM904 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34207] Nucleotide sequences of the VGAM904 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM904 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM904 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM904 are further

described hereinbelow with reference to Table 1.

[34208] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM904 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM904 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34209] As mentioned hereinabove with reference to Fig. 1, a function of VGAM904 gene, herein designated VGAM is inhibition of expression of VGAM904 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM904 correlate with, and may be deduced from, the identity of the target genes which VGAM904 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34210] CARPX (Accession NM\_020178) is a VGAM904 host target gene. CARPX BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CARPX, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CARPX BINDING SITE, designated SEQ

ID:21394, to the nucleotide sequence of VGAM904 RNA, herein designated VGAM RNA, also designated SEQ ID:3615.

[34211] A function of VGAM904 is therefore inhibition of CARPX (Accession NM\_020178), a gene which is alpha-carbonic anhydrases-related protein. Accordingly, utilities of VGAM904 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CARPX. The function of CARPX has been established by previous studies. Hewett-Emmett and Tashian (1996) described an alignment of 6 human brain ESTs that encode part of an alpha-carbonic anhydrase, which they named CA X. They noted that gln92, his94, and his119, which are invariant in all alpha-CA isozymes with catalytic activity, were replaced by glu, arg, and gln, respectively. They therefore suggested that CA X might represent a new CA-related protein (CA-RP). In reporting the sequence of partial CA XI (OMIM Ref. No. 604644) cDNAs from human and mouse, Lovejoy et al. (1998) stated that these sequences were most homologous to the human CA X sequence. They reported an extended but incomplete human CA X protein sequence of 169 amino acids that was based on exons in a BAC clone containing human genomic DNA from chro-

mosome 17 (GenBank AC002090) and 5 additional human ESTs.

[34212] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34213] Hewett-Emmett, D.; Tashian, R. E. : Functional diversity, conservation, and convergence in the evolution of the alpha-, beta-, and gamma-carbonic anhydrase gene families. *Molec. Phylogenet. Evol.* 5: 50-77, 1996. ; and

[34214] Lovejoy, D. A.; Hewett-Emmett, D.; Porter, C. A.; Cepoi, D.; Sheffield, A.; Vale, W. W.; Tashian, R. E. : Evolutionarily conserved, 'acatalytic' carbonic anhydrase-related protein XI con.

[34215] Further studies establishing the function and utilities of CARPX are found in John Hopkins OMIM database record ID 604642, and in cited publications numbered 6935-6938 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Interferon (alpha, beta and omega) Receptor 1 (IFNAR1, Accession NM\_000629) is another VGAM904 host target gene. IFNAR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IFNAR1, corresponding to a HOST TARGET binding site such as

BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IFNAR1 BINDING SITE, designated SEQ ID:6245, to the nucleotide sequence of VGAM904 RNA, herein designated VGAM RNA, also designated SEQ ID:3615.

[34216] Another function of VGAM904 is therefore inhibition of Interferon (alpha, beta and omega) Receptor 1 (IFNAR1, Accession NM\_000629), a gene which is a receptor for interferons alpha and beta. Accordingly, utilities of VGAM904 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IFNAR1. The function of IFNAR1 has been established by previous studies. Alpha-type antiviral protein is a factor, presumably protein in nature, that mediates specific interferon inhibition of virus replication. According to studies of mouse-man hybrid clones, the locus determining this protein is carried on chromosome 21 (Tan et al., 1973). Tan et al. (1974) made observations of dosage effect in monosomy-21 and trisomy-21 cells which supported assignment of the locus to chromosome 21. This character was also called interferon sensitivity (IS). Chany et al. (1975) showed that trisomy-21 cells have increased interferon sensitivity. Trisomy-16 cells have reduced sensitiv-

ity. This might suggest the presence on chromosome 16 of a regulator of mouse antiviral protein. Revel et al. (1976) showed that antibody to a cell surface component coded by human chromosome 21 inhibited the action of interferon. This suggested that antiviral protein is an interferon receptor. See 147570, 147640, 147660 for a discussion of the gamma, beta, and alpha interferons, respectively. De Clercq et al. (1976) concluded that it is not a cell membrane receptor for interferon that is encoded by chromosome 21. Cellular responses to cytokines involve cross-communication through their respective receptors. The IFNs alpha, beta, and gamma mediate innate immune responses to viral infection through IFNAR1/IFNAR2 (OMIM Ref. No. 602376) for IFNA and IFNB, and IFNGR1 (OMIM Ref. No. 107470)/IFNGR2 (OMIM Ref. No. 147569) for IFNG. Stimulation of these receptors activates Janus protein kinases (e.g., JAK1, 147795 and JAK2, 147796), which leads to the tyrosine phosphorylation of STAT1 (OMIM Ref. No. 600555) and STAT2 (OMIM Ref. No. 600556). Although the IFN receptors are expressed at low levels in cells, they may be clustered in the cell membrane to permit efficient signal transduction. Using mouse embryonic fibroblasts (MEFs) from IFNAR1- and



IFNGR1-deficient mice, Takaoka et al. (2000) observed that the STAT1-mediated DNA-binding activity and the antiviral response to IFNG in IFNAR-null MEFs but not to IFNA in IFNGR-null MEFs are impaired. Restoration of the IFNG response requires constitutive subthreshold IFNA/IFNB signaling and an intact IFNAR1 capable of interacting with STAT1 after tyrosine phosphorylation. Immunoblot analysis showed that IFNAR1 coimmunoprecipitated with the nonligand-binding component, IFNGR2, of the IFNGR complex in wildtype MEFs but less well in IFNB-null MEFs. Immunoblot analysis also demonstrated that the IFN receptor components are exclusively localized in the caveolar membrane fractions (see OMIM Ref. No. CAV1; 601047) where there is a concentration of cytoplasmically oriented signaling molecules

[34217] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34218] Takaoka, A.; Mitani, Y.; Suemori, H.; Sato, M.; Yokochi, T.; Noguchi, S.; Tanaka, N.; Taniguchi, T. : Cross talk between interferon-gamma and -alpha/beta signaling components in caveolar membrane domains. Science 288: 2357-2360, 2000. ; and

[34219] Revel, M.; Bash, D.; Ruddle, F. H. : Antibodies to a cell-surface component coded by human chromosome 21 inhibit action of interferon. Nature 260: 139-141, 1976.

[34220] Further studies establishing the function and utilities of IFNAR1 are found in John Hopkins OMIM database record ID 107450, and in cited publications numbered 12523-11826, 2737, 3910, 11827-1183 and 3643-3651 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. KIAA0318 (Accession XM\_044334) is another VGAM904 host target gene. KIAA0318 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0318, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0318 BINDING SITE, designated SEQ ID:34183, to the nucleotide sequence of VGAM904 RNA, herein designated VGAM RNA, also designated SEQ ID:3615.

[34221] Another function of VGAM904 is therefore inhibition of KIAA0318 (Accession XM\_044334). Accordingly, utilities of VGAM904 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA0318. LOC160414 (Accession XM\_100898) is another VGAM904 host target gene. LOC160414 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC160414, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC160414 BINDING SITE, designated SEQ ID:42102, to the nucleotide sequence of VGAM904 RNA, herein designated VGAM RNA, also designated SEQ ID:3615.

[34222] Another function of VGAM904 is therefore inhibition of LOC160414 (Accession XM\_100898). Accordingly, utilities of VGAM904 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC160414. LOC57086 (Accession NM\_020351) is another VGAM904 host target gene. LOC57086 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC57086, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57086 BINDING SITE, designated SEQ ID:21615, to the nucleotide sequence of VGAM904 RNA, herein designated

VGAM RNA, also designated SEQ ID:3615.

[34223] Another function of VGAM904 is therefore inhibition of LOC57086 (Accession NM\_020351). Accordingly, utilities of VGAM904 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57086. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 905 (VGAM905) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34224] VGAM905 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM905 was detected is described hereinabove with reference to Figs. 1–8.

[34225] VGAM905 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saimiriine Herpesvirus 2. VGAM905 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34226] VGAM905 gene encodes a VGAM905 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM905 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM905 precursor RNA is designated SEQ ID:891, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:891 is located at position 79238 relative to the genome of Saimiriine Herpesvirus 2.

[34227] VGAM905 precursor RNA folds onto itself, forming VGAM905 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34228] An enzyme complex designated DICER COMPLEX, `dices` the VGAM905 folded precursor RNA into VGAM905 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM905 RNA is designated SEQ ID:3616, and is provided hereinbelow with reference to the sequence listing part.

[34229] VGAM905 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM905 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM905 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34230] VGAM905 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM905 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM905 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM905 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM905 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34231] The complementary binding of VGAM905 RNA, herein designated VGAM RNA, to host target binding sites on VGAM905 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM905 host target RNA into VGAM905 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34232] It is appreciated that VGAM905 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM905 host target genes. The mRNA of

each one of this plurality of VGAM905 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM905 RNA, herein designated VGAM RNA, and which when bound by VGAM905 RNA causes inhibition of translation of respective one or more VGAM905 host target proteins.

[34233] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM905 gene, herein designated VGAM GENE, on one or more VGAM905 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science



294,779 (2001)).

[34234] It is yet further appreciated that a function of VGAM905 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of viral infection by Saimiriine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM905 correlate with, and may be deduced from, the identity of the host target genes which VGAM905 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34235] Nucleotide sequences of the VGAM905 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM905 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM905 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM905 are further described hereinbelow with reference to Table 1.

[34236] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM905 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM905 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[34237] As mentioned hereinabove with reference to Fig. 1, a function of VGAM905 gene, herein designated VGAM is inhibition of expression of VGAM905 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM905 correlate with, and may be deduced from, the identity of the target genes which VGAM905 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34238] ABH (Accession XM\_007409) is a VGAM905 host target gene. ABH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ABH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ABH BINDING SITE, designated SEQ ID:30056, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34239] A function of VGAM905 is therefore inhibition of ABH (Accession XM\_007409). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ABH. Brain

and Acute Leukemia, Cytoplasmic (BAALC, Accession NM\_024812) is another VGAM905 host target gene. BAALC BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by BAALC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BAALC BINDING SITE, designated SEQ ID:24195, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34240] Another function of VGAM905 is therefore inhibition of Brain and Acute Leukemia, Cytoplasmic (BAALC, Accession NM\_024812). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BAALC. CD34 Antigen (CD34, Accession NM\_001773) is another VGAM905 host target gene. CD34 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CD34, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD34 BINDING SITE, designated SEQ

ID:7537, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34241] Another function of VGAM905 is therefore inhibition of CD34 Antigen (CD34, Accession NM\_001773), a gene which is a monomeric cell surface antigen that is selectively expressed on human hematopoietic progenitor cells. Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD34. The function of CD34 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM55. Deoxycytidine Kinase (DCK, Accession NM\_000788) is another VGAM905 host target gene. DCK BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DCK, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DCK BINDING SITE, designated SEQ ID:6443, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34242] Another function of VGAM905 is therefore inhibition of

Deoxycytidine Kinase (DCK, Accession NM\_000788), a gene which mediates the phosphorylation of several deoxyribonucleosides and their analogs. Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DCK. The function of DCK and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM538. Fatty-acid-Coenzyme A Ligase, Long-chain 4 (FACL4, Accession NM\_022977) is another VGAM905 host target gene. FACL4 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FACL4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FACL4 BINDING SITE, designated SEQ ID:23255, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34243] Another function of VGAM905 is therefore inhibition of Fatty-acid-Coenzyme A Ligase, Long-chain 4 (FACL4, Accession NM\_022977). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases

and clinical conditions associated with FACL4. FREB (Accession NM\_032738) is another VGAM905 host target gene. FREB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FREB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FREB BINDING SITE, designated SEQ ID:26466, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34244] Another function of VGAM905 is therefore inhibition of FREB (Accession NM\_032738). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FREB. Interleukin 1 Receptor, Type I (IL1R1, Accession NM\_000877) is another VGAM905 host target gene. IL1R1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL1R1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL1R1 BINDING SITE, designated SEQ ID:6563, to the nucleotide sequence of VGAM905 RNA, herein designated

VGAM RNA, also designated SEQ ID:3616.

[34245] Another function of VGAM905 is therefore inhibition of Interleukin 1 Receptor, Type I (IL1R1, Accession NM\_000877), a gene which is a receptor for interleukin-1 alpha (il-1a), beta (il-1b), and interleukin-1 receptor antagonist protein (il-1ra). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL1R1. The function of IL1R1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM704. Junctional Adhesion Molecule 3 (JAM3, Accession NM\_032801) is another VGAM905 host target gene. JAM3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JAM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JAM3 BINDING SITE, designated SEQ ID:26555, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34246] Another function of VGAM905 is therefore inhibition of Junctional Adhesion Molecule 3 (JAM3, Accession

NM\_032801), a gene which is a member of the junctional adhesion molecule protein family. Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JAM3. The function of JAM3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200. Nuclear Receptor Coactivator 3 (NCOA3, Accession NM\_006534) is another VGAM905 host target gene. NCOA3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NCOA3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NCOA3 BINDING SITE, designated SEQ ID:13283, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34247] Another function of VGAM905 is therefore inhibition of Nuclear Receptor Coactivator 3 (NCOA3, Accession NM\_006534), a gene which directly binds nuclear receptors and stimulates the transcriptional activities in hormone-dependent fashion. Accordingly, utilities of



VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NCOA3. The function of NCOA3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM215. Nuclear Receptor Interacting Protein 1 (NRIP1, Accession XM\_009699) is another VGAM905 host target gene. NRIP1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NRIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NRIP1 BINDING SITE, designated SEQ ID:30122, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34248] Another function of VGAM905 is therefore inhibition of Nuclear Receptor Interacting Protein 1 (NRIP1, Accession XM\_009699), a gene which modulates transcriptional activation by the estrogen receptor. Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NRIP1. The function of NRIP1 and its association with various dis-

eases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM276. Prominin-like 1 (mouse) (PROML1, Accession NM\_006017) is another VGAM905 host target gene.

PROML1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PROML1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PROML1 BINDING SITE, designated SEQ ID:12634, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34249] Another function of VGAM905 is therefore inhibition of Prominin-like 1 (mouse) (PROML1, Accession NM\_006017), a gene which is a Transmembrane protein. Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PROML1. The function of PROML1 has been established by previous studies. the prominin 5-transmembrane domain glycoprotein was originally identified as a protein that selectively localized at the apical surface of murine neuroepithelial cells, whereas

PROML1 was identified as an antigenic marker (AC133 antigen) in hematopoietic stem cells (Miraglia et al., 1997; Yin et al., 1997) and found to be expressed in retinoblastoma cell lines and adult retina. Most of the PROML1 gene is contained in 23 exons distributed over more than 50 kb of genomic sequence. The gene is predicted to encode an 865-amino acid glycoprotein. Prominin is conserved throughout the animal kingdom. Photoreceptors are the cells in the retina that are responsible for generation of the neuronal signal in response to light. The outer segments of vertebrate photoreceptors house a stack of photoreceptive membranes called disks. These membranes have a high rate of turnover. Disks of vertebrate photoreceptors are produced at the base of the outer segments initially by evagination of the plasma membrane with subsequent rim formation and membrane fusion resulting in release of the individual disks into the cytoplasm. The disks are ultimately shed from the terminal end of the outer segment and phagocytosed by the retinal pigment epithelium. A similar, although not identical process appears to occur in cone photoreceptor disks. Because of their origin from the plasma membranes, genes that encode retinal proteins targeted to plasma membrane pro-

trusions represent candidates for inherited retinal degenerations. One such candidate is the gene encoding human PROML1. Murine prominin (prom) shows a strong preference for plasma membrane protrusions in a variety of epithelial cells, whereas PROML1 is expressed in retinoblastoma cell lines and adult retina. Maw et al. (2000) performed molecular genetic analyses on an Indian pedigree segregating for autosomal recessive retinal degeneration and found that affected individuals were homozygous for deletion of nucleotide 1878 (a G) in PROML1 (604365.0001). This alteration was predicted to result in a frameshift at codon 614 with premature termination of translation. Expression of a similar prom deletion mutant in CHO cells indicated that the truncated protein does not reach the cell surface. Immunocytochemistry indicated that prom is concentrated in the plasma membrane evaginations at the base of the outer segments of rod photoreceptors. These findings suggested that loss of prominin causes retinal degeneration, possibly because of impaired generation of the evaginations and/or impaired conversion of the evaginations to disks. In the family in which Maw et al. (2000) found the deletion mutation in PROML1, 4 of 8 children were affected, the offspring of an uncle-

niece marriage. Linkage studies localized the mutant gene to 4p. Two-point linkage analysis using the deletion mutation gave a peak lod score of 3.17 at  $\theta = 0.00$ .

Markers distal to D4S1602 formed a haplotype that cosegregated with the disorder. Crossovers indicated that the critical region was proximal to D4S2960 and distal to D4S1567. This region was found to be distinct from the distal PDEB (OMIM Ref. No. 180072) region at 4p16.3 and the proximal CNGA1 (OMIM Ref. No. 123825) region at 4p12-cen; both of these genes had previously been implicated in autosomal recessive retinal degeneration.

[34250] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34251] Maw, M. A.; Corbeil, D.; Koch, J.; Hellwig, A.; Wilson-Wheeler, J. C.; Bridges, R. J.; Kumaramanickavel, G.; John, S.; Nancarrow, D.; Roper, K.; Weigmann, A.; Huttner, W. B.; Denton, M. J. : A frameshift mutation in prominin (mouse)-like 1 causes human retinal degeneration. *Hum. Molec. Genet.* 9: 27-34, 2000. ; and

[34252] Miraglia, S.; Godfrey, W.; Yin, A. H.; Atkins, K.; Warnke, R.; Holden, J. T.; Bray, R. A.; Waller, E. K.; Buck, D. W. : A novel five-transmembrane hematopoietic stem cell anti-

gen: isola.

[34253] Further studies establishing the function and utilities of PROML1 are found in John Hopkins OMIM database record ID 604365, and in cited publications numbered 5316–5318 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RGL (Accession NM\_015149) is another VGAM905 host target gene. RGL BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RGL, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RGL BINDING SITE, designated SEQ ID:17505, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34254] Another function of VGAM905 is therefore inhibition of RGL (Accession NM\_015149), a gene which is involved in nucleotide exchange factor. Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RGL. The function of RGL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to

VGAM861.Angiomotin (AMOT, Accession NM\_133265) is another VGAM905 host target gene. AMOT BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AMOT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AMOT BINDING SITE, designated SEQ ID:28420, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34255] Another function of VGAM905 is therefore inhibition of Angiomotin (AMOT, Accession NM\_133265). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AMOT. ARSDR1 (Accession NM\_016026) is another VGAM905 host target gene. ARSDR1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by ARSDR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARSDR1 BINDING SITE, designated SEQ ID:18111, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA,

also designated SEQ ID:3616.

[34256] Another function of VGAM905 is therefore inhibition of ARSDR1 (Accession NM\_016026). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARSDR1. FLJ12171 (Accession NM\_024619) is another VGAM905 host target gene. FLJ12171 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ12171, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12171 BINDING SITE, designated SEQ ID:23880, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34257] Another function of VGAM905 is therefore inhibition of FLJ12171 (Accession NM\_024619). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12171. Glutamate Receptor, Ionotropic, Delta 1 (GRID1, Accession XM\_043613) is another VGAM905 host target gene. GRID1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GRID1, cor-



responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GRID1 BINDING SITE, designated SEQ ID:33977, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34258] Another function of VGAM905 is therefore inhibition of Glutamate Receptor, Ionotropic, Delta 1 (GRID1, Accession XM\_043613). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GRID1. KIAA0332 (Accession XM\_031553) is another VGAM905 host target gene. KIAA0332 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0332, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0332 BINDING SITE, designated SEQ ID:31417, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34259] Another function of VGAM905 is therefore inhibition of KIAA0332 (Accession XM\_031553). Accordingly, utilities

of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0332. KIAA0556 (Accession XM\_044632) is another VGAM905 host target gene. KIAA0556 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0556, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0556 BINDING SITE, designated SEQ ID:34248, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34260] Another function of VGAM905 is therefore inhibition of KIAA0556 (Accession XM\_044632). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0556. KIAA0826 (Accession XM\_093839) is another VGAM905 host target gene. KIAA0826 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0826, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

KIAA0826 BINDING SITE, designated SEQ ID:40214, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34261] Another function of VGAM905 is therefore inhibition of KIAA0826 (Accession XM\_093839). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0826. KIAA0977 (Accession NM\_014900) is another VGAM905 host target gene. KIAA0977 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0977, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0977 BINDING SITE, designated SEQ ID:17080, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34262] Another function of VGAM905 is therefore inhibition of KIAA0977 (Accession NM\_014900). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0977. KIAA1041 (Accession NM\_014947) is another VGAM905 host target gene. KIAA1041 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1041, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1041 BINDING SITE, designated SEQ ID:17265, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34263] Another function of VGAM905 is therefore inhibition of KIAA1041 (Accession NM\_014947). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1041. KIAA1238 (Accession XM\_048675) is another VGAM905 host target gene. KIAA1238 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1238, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1238 BINDING SITE, designated SEQ ID:35215, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34264] Another function of VGAM905 is therefore inhibition of

KIAA1238 (Accession XM\_048675). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1238. Methionyl Aminopeptidase 1 (METAP1, Accession XM\_052334) is another VGAM905 host target gene. METAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by METAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of METAP1 BINDING SITE, designated SEQ ID:35958, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34265] Another function of VGAM905 is therefore inhibition of Methionyl Aminopeptidase 1 (METAP1, Accession XM\_052334). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with METAP1. NIN283 (Accession NM\_032268) is another VGAM905 host target gene. NIN283 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NIN283, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NIN283 BINDING SITE, designated SEQ ID:26015, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34266] Another function of VGAM905 is therefore inhibition of NIN283 (Accession NM\_032268). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NIN283. PRO1331 (Accession NM\_030778) is another VGAM905 host target gene. PRO1331 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO1331, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO1331 BINDING SITE, designated SEQ ID:25067, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34267] Another function of VGAM905 is therefore inhibition of PRO1331 (Accession NM\_030778). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with PRO1331. Serine Threonine Kinase 39 (STE20/SPS1 homolog, yeast) (STK39, Accession NM\_013233) is another VGAM905 host target gene. STK39 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by STK39, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STK39 BINDING SITE, designated SEQ ID:14891, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34268] Another function of VGAM905 is therefore inhibition of Serine Threonine Kinase 39 (STE20/SPS1 homolog, yeast) (STK39, Accession NM\_013233). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STK39. TRIP-Br2 (Accession NM\_014755) is another VGAM905 host target gene. TRIP-Br2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TRIP-Br2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of TRIP-Br2 BINDING SITE, designated SEQ ID:16493, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34269] Another function of VGAM905 is therefore inhibition of TRIP-Br2 (Accession NM\_014755). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIP-Br2. LOC120856 (Accession XM\_058509) is another VGAM905 host target gene. LOC120856 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120856, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120856 BINDING SITE, designated SEQ ID:36633, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34270] Another function of VGAM905 is therefore inhibition of LOC120856 (Accession XM\_058509). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120856. LOC120939 (Accession XM\_073688) is an-



other VGAM905 host target gene. LOC120939 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC120939, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC120939 BINDING SITE, designated SEQ ID:37510, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34271] Another function of VGAM905 is therefore inhibition of LOC120939 (Accession XM\_073688). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC120939. LOC130612 (Accession XM\_059461) is another VGAM905 host target gene. LOC130612 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC130612, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC130612 BINDING SITE, designated SEQ ID:36997, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34272] Another function of VGAM905 is therefore inhibition of LOC130612 (Accession XM\_059461). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC130612. LOC148936 (Accession XM\_097556) is another VGAM905 host target gene. LOC148936 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148936, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148936 BINDING SITE, designated SEQ ID:40931, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34273] Another function of VGAM905 is therefore inhibition of LOC148936 (Accession XM\_097556). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148936. LOC148938 (Accession XM\_097555) is another VGAM905 host target gene. LOC148938 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148938, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148938 BINDING SITE, designated SEQ ID:40924, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34274] Another function of VGAM905 is therefore inhibition of LOC148938 (Accession XM\_097555). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148938. LOC221504 (Accession XM\_166476) is another VGAM905 host target gene. LOC221504 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC221504, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221504 BINDING SITE, designated SEQ ID:44396, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34275] Another function of VGAM905 is therefore inhibition of LOC221504 (Accession XM\_166476). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

LOC221504. LOC91151 (Accession NM\_033208) is another VGAM905 host target gene. LOC91151 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC91151, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC91151 BINDING SITE, designated SEQ ID:27056, to the nucleotide sequence of VGAM905 RNA, herein designated VGAM RNA, also designated SEQ ID:3616.

[34276] Another function of VGAM905 is therefore inhibition of LOC91151 (Accession NM\_033208). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC91151. LOC92391 (Accession XM\_044793) is another VGAM905 host target gene. LOC92391 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92391, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92391 BINDING SITE, designated SEQ ID:34273, to the nucleotide sequence of VGAM905 RNA, herein designated

VGAM RNA, also designated SEQ ID:3616.

[34277] Another function of VGAM905 is therefore inhibition of LOC92391 (Accession XM\_044793). Accordingly, utilities of VGAM905 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92391. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 906 (VGAM906) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34278] VGAM906 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM906 was detected is described hereinabove with reference to Figs. 1–8.

[34279] VGAM906 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saimiriine Herpesvirus 2. VGAM906 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34280] VGAM906 gene encodes a VGAM906 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM906 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM906 precursor RNA is designated SEQ ID:892, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:892 is located at position 77662 relative to the genome of Saimiriine Herpesvirus 2.

[34281] VGAM906 precursor RNA folds onto itself, forming VGAM906 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34282] An enzyme complex designated DICER COMPLEX, `dices` the VGAM906 folded precursor RNA into VGAM906 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 43%) nucleotide sequence of VGAM906 RNA is designated SEQ ID:3617, and is provided hereinbelow with reference to the sequence listing part.

[34283] VGAM906 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM906 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM906 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[34284] VGAM906 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM906 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM906 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM906 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM906 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[34285] The complementary binding of VGAM906 RNA, herein designated VGAM RNA, to host target binding sites on VGAM906 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM906 host target RNA into VGAM906 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34286] It is appreciated that VGAM906 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM906 host target genes. The mRNA of



each one of this plurality of VGAM906 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM906 RNA, herein designated VGAM RNA, and which when bound by VGAM906 RNA causes inhibition of translation of respective one or more VGAM906 host target proteins.

[34287] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM906 gene, herein designated VGAM GENE, on one or more VGAM906 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[34288] It is yet further appreciated that a function of VGAM906 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of viral infection by Saimiriine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM906 correlate with, and may be deduced from, the identity of the host target genes which VGAM906 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34289] Nucleotide sequences of the VGAM906 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM906 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM906 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM906 are further described hereinbelow with reference to Table 1.

[34290] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM906 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM906 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[34291] As mentioned hereinabove with reference to Fig. 1, a function of VGAM906 gene, herein designated VGAM is inhibition of expression of VGAM906 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM906 correlate with, and may be deduced from, the identity of the target genes which VGAM906 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34292] UDP-glucose Dehydrogenase (UGDH, Accession NM\_003359) is a VGAM906 host target gene. UGDH BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UGDH, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UGDH BINDING SITE, designated SEQ ID:9387, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34293] A function of VGAM906 is therefore inhibition of UDP-glucose Dehydrogenase (UGDH, Accession NM\_003359), a gene which is an UDP-glucose dehydrogenase. Accord-

ingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UGDH. The function of UGDH and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74. Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736) is another VGAM906 host target gene. XPR1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by XPR1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of XPR1 BINDING SITE, designated SEQ ID:11122, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34294] Another function of VGAM906 is therefore inhibition of Xenotropic and Polytopic Retrovirus Receptor (XPR1, Accession NM\_004736), a gene which is a putative G protein-coupled receptor and a target for xenotropic and polytropic murine leukemia retroviruses. Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated

with XPR1. The function of XPR1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM430. AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Accession NM\_007247) is another VGAM906 host target gene. AP1GBP1 BINDING SITE1 through AP1GBP1 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by AP1GBP1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP1GBP1 BINDING SITE1 through AP1GBP1 BINDING SITE3, designated SEQ ID:14115, SEQ ID:27877 and SEQ ID:27870 respectively, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34295] Another function of VGAM906 is therefore inhibition of AP1 Gamma Subunit Binding Protein 1 (AP1GBP1, Accession NM\_007247). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP1GBP1. FLJ12598 (Accession NM\_024754) is another VGAM906 host target gene. FLJ12598 BINDING SITE is HOST TARGET binding

site found in the 5` untranslated region of mRNA encoded by FLJ12598, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ12598 BINDING SITE, designated SEQ ID:24097, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34296] Another function of VGAM906 is therefore inhibition of FLJ12598 (Accession NM\_024754). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ12598. FLJ21140 (Accession NM\_024776) is another VGAM906 host target gene. FLJ21140 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ21140, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ21140 BINDING SITE, designated SEQ ID:24141, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34297] Another function of VGAM906 is therefore inhibition of

FLJ21140 (Accession NM\_024776). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ21140. High-mobility Group (nonhistone chromosomal) Protein 17-like 1 (HMG17L1, Accession NM\_021024) is another VGAM906 host target gene. HMG17L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HMG17L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HMG17L1 BINDING SITE, designated SEQ ID:22014, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34298] Another function of VGAM906 is therefore inhibition of High-mobility Group (nonhistone chromosomal) Protein 17-like 1 (HMG17L1, Accession NM\_021024). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HMG17L1. Myoneurin (MYNN, Accession NM\_018657) is another VGAM906 host target gene. MYNN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MYNN, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYNN BINDING SITE, designated SEQ ID:20725, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34299] Another function of VGAM906 is therefore inhibition of Myoneurin (MYNN, Accession NM\_018657). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYNN. Nucleosome Assembly Protein 1-like 1 (NAP1L1, Accession NM\_139207) is another VGAM906 host target gene. NAP1L1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NAP1L1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAP1L1 BINDING SITE, designated SEQ ID:29224, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34300] Another function of VGAM906 is therefore inhibition of Nucleosome Assembly Protein 1-like 1 (NAP1L1, Acces-



sion NM\_139207). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAP1L1. LOC146050 (Accession XM\_085301) is another VGAM906 host target gene. LOC146050 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC146050, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC146050 BINDING SITE, designated SEQ ID:38055, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34301] Another function of VGAM906 is therefore inhibition of LOC146050 (Accession XM\_085301). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC146050. LOC158549 (Accession XM\_098963) is another VGAM906 host target gene. LOC158549 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158549, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC158549 BINDING SITE, designated SEQ ID:42009, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34302] Another function of VGAM906 is therefore inhibition of LOC158549 (Accession XM\_098963). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158549. LOC169166 (Accession XM\_095541) is another VGAM906 host target gene. LOC169166 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC169166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169166 BINDING SITE, designated SEQ ID:40271, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34303] Another function of VGAM906 is therefore inhibition of LOC169166 (Accession XM\_095541). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC169166. LOC199957 (Accession XM\_114068) is an-

other VGAM906 host target gene. LOC199957 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC199957, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199957 BINDING SITE, designated SEQ ID:42671, to the nucleotide sequence of VGAM906 RNA, herein designated VGAM RNA, also designated SEQ ID:3617.

[34304] Another function of VGAM906 is therefore inhibition of LOC199957 (Accession XM\_114068). Accordingly, utilities of VGAM906 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199957. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 907 (VGAM907) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34305] VGAM907 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM907 was detected is described

hereinabove with reference to Figs. 1–8.

[34306] VGAM907 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Saimiriine Herpesvirus 2. VGAM907 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34307] VGAM907 gene encodes a VGAM907 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM907 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM907 precursor RNA is designated SEQ ID:893, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:893 is located at position 79366 relative to the genome of Saimiriine Herpesvirus 2.

[34308] VGAM907 precursor RNA folds onto itself, forming VGAM907 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an

accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34309] An enzyme complex designated DICER COMPLEX, `dices` the VGAM907 folded precursor RNA into VGAM907 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 46%) nucleotide sequence of VGAM907 RNA is designated SEQ ID:3618, and is provided hereinbelow with reference to the sequence listing part.

[34310] VGAM907 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM907 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM907 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34311] VGAM907 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites lo-

cated in untranslated regions of VGAM907 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM907 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM907 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM907 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34312] The complementary binding of VGAM907 RNA, herein designated VGAM RNA, to host target binding sites on VGAM907 host target RNA, herein designated VGAM HOST

TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM907 host target RNA into VGAM907 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34313] It is appreciated that VGAM907 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM907 host target genes. The mRNA of each one of this plurality of VGAM907 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM907 RNA, herein designated VGAM RNA, and which when bound by VGAM907 RNA causes inhibition of translation of respective one or more VGAM907 host target proteins.

[34314] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM907 gene, herein designated VGAM GENE, on one or more VGAM907 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a spe-

cific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34315] It is yet further appreciated that a function of VGAM907 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM907 include diagnosis, prevention and treatment of viral infection by Saimiriine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM907 correlate with, and may be deduced from, the identity of the host target genes which VGAM907 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34316] Nucleotide sequences of the VGAM907 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM907 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding



of VGAM907 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM907 are further described hereinbelow with reference to Table 1.

[34317] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM907 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM907 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34318] As mentioned hereinabove with reference to Fig. 1, a function of VGAM907 gene, herein designated VGAM is inhibition of expression of VGAM907 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM907 correlate with, and may be deduced from, the identity of the target genes which VGAM907 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34319] HCA4 (Accession XM\_085287) is a VGAM907 host target gene. HCA4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HCA4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Ta-

ble 2 illustrates the complementarity of the nucleotide sequences of HCA4 BINDING SITE, designated SEQ ID:38022, to the nucleotide sequence of VGAM907 RNA, herein designated VGAM RNA, also designated SEQ ID:3618.

[34320] A function of VGAM907 is therefore inhibition of HCA4 (Accession XM\_085287). Accordingly, utilities of VGAM907 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCA4. KIAA1600 (Accession XM\_049351) is another VGAM907 host target gene. KIAA1600 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1600, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1600 BINDING SITE, designated SEQ ID:35391, to the nucleotide sequence of VGAM907 RNA, herein designated VGAM RNA, also designated SEQ ID:3618.

[34321] Another function of VGAM907 is therefore inhibition of KIAA1600 (Accession XM\_049351). Accordingly, utilities of VGAM907 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1600. Purinergic Receptor P2X-like 1, Orphan Recep-

tor (P2RXL1, Accession NM\_005446) is another VGAM907 host target gene. P2RXL1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by P2RXL1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of P2RXL1 BINDING SITE, designated SEQ ID:11933, to the nucleotide sequence of VGAM907 RNA, herein designated VGAM RNA, also designated SEQ ID:3618.

[34322] Another function of VGAM907 is therefore inhibition of Purinergic Receptor P2X-like 1, Orphan Receptor (P2RXL1, Accession NM\_005446). Accordingly, utilities of VGAM907 include diagnosis, prevention and treatment of diseases and clinical conditions associated with P2RXL1.

LOC133418 (Accession XM\_059649) is another VGAM907 host target gene. LOC133418 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC133418, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC133418 BINDING SITE, designated SEQ ID:37038, to the nucleotide se-

quence of VGAM907 RNA, herein designated VGAM RNA, also designated SEQ ID:3618.

[34323] Another function of VGAM907 is therefore inhibition of LOC133418 (Accession XM\_059649). Accordingly, utilities of VGAM907 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC133418. LOC153222 (Accession XM\_087631) is another VGAM907 host target gene. LOC153222 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153222, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153222 BINDING SITE, designated SEQ ID:39369, to the nucleotide sequence of VGAM907 RNA, herein designated VGAM RNA, also designated SEQ ID:3618.

[34324] Another function of VGAM907 is therefore inhibition of LOC153222 (Accession XM\_087631). Accordingly, utilities of VGAM907 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153222. LOC255098 (Accession XM\_170912) is another VGAM907 host target gene. LOC255098 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC255098, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255098 BINDING SITE, designated SEQ ID:45687, to the nucleotide sequence of VGAM907 RNA, herein designated VGAM RNA, also designated SEQ ID:3618.

[34325] Another function of VGAM907 is therefore inhibition of LOC255098 (Accession XM\_170912). Accordingly, utilities of VGAM907 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255098. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 908 (VGAM908) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34326] VGAM908 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM908 was detected is described hereinabove with reference to Figs. 1–8.

[34327] VGAM908 gene, herein designated VGAM GENE, is a viral

gene contained in the genome of Saimiriine Herpesvirus 2. VGAM908 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34328] VGAM908 gene encodes a VGAM908 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM908 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM908 precursor RNA is designated SEQ ID:894, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:894 is located at position 78640 relative to the genome of Saimiriine Herpesvirus 2.

[34329] VGAM908 precursor RNA folds onto itself, forming VGAM908 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34330] An enzyme complex designated DICER COMPLEX, `dices` the VGAM908 folded precursor RNA into VGAM908 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 76%) nucleotide sequence of VGAM908 RNA is designated SEQ ID:3619, and is provided hereinbelow with reference to the sequence listing part.

[34331] VGAM908 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM908 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM908 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34332] VGAM908 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM908 host target RNA, herein designated VGAM HOST TARGET RNA. This

complementary binding is due to the fact that the nucleotide sequence of VGAM908 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM908 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM908 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34333] The complementary binding of VGAM908 RNA, herein designated VGAM RNA, to host target binding sites on VGAM908 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM908 host tar-



get RNA into VGAM908 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34334] It is appreciated that VGAM908 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM908 host target genes. The mRNA of each one of this plurality of VGAM908 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM908 RNA, herein designated VGAM RNA, and which when bound by VGAM908 RNA causes inhibition of translation of respective one or more VGAM908 host target proteins.

[34335] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM908 gene, herein designated VGAM GENE, on one or more VGAM908 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4

and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34336] It is yet further appreciated that a function of VGAM908 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of viral infection by Saimiriine Herpesvirus 2. Specific functions, and accordingly utilities, of VGAM908 correlate with, and may be deduced from, the identity of the host target genes which VGAM908 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34337] Nucleotide sequences of the VGAM908 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM908 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM908 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM908 are further

described hereinbelow with reference to Table 1.

[34338] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM908 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM908 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34339] As mentioned hereinabove with reference to Fig. 1, a function of VGAM908 gene, herein designated VGAM is inhibition of expression of VGAM908 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM908 correlate with, and may be deduced from, the identity of the target genes which VGAM908 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34340] Eyes Absent Homolog 1 (Drosophila) (EYA1, Accession NM\_000503) is a VGAM908 host target gene. EYA1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by EYA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EYA1

BINDING SITE, designated SEQ ID:6115, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34341] A function of VGAM908 is therefore inhibition of Eyes Absent Homolog 1 (Drosophila) (EYA1, Accession NM\_000503). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EYA1. Gamma-glutamyltransferase 1 (GGT1, Accession NM\_013421) is another VGAM908 host target gene. GGT1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GGT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GGT1 BINDING SITE, designated SEQ ID:15081, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34342] Another function of VGAM908 is therefore inhibition of Gamma-glutamyltransferase 1 (GGT1, Accession NM\_013421), a gene which catalyzes the transfer of the glutamyl moiety of glutathione to a variety of amino acids and dipeptide acceptors. Accordingly, utilities of

VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GGT1.

The function of GGT1 has been established by previous studies. Gamma-glutamyltranspeptidase (EC 2.3.2.2) acts as a glutathionase and catalyzes the transfer of the glutamyl moiety of glutathione to a variety of amino acids and dipeptide acceptors. This enzyme is located on the outer surface of the cell membrane. It is widely distributed in mammalian tissues involved in absorption and secretion. In humans, hepatic GGT activity is elevated in some liver diseases. GGT is released into the bloodstream after liver damage, and an elevated level of the enzyme may be a useful early sign of hepatocellular carcinoma. Schulman et al. (1975) described a mildly retarded adult male with glutathionemia and marked glutathionuria, whose cultured skin fibroblasts showed very low activity of the transpeptidase. Since several studies have suggested that the transpeptidase may play a role in cellular amino acid transport, the lack of aminoaciduria and aminoacidemia was noteworthy. O'Daley (1968) may have described the same condition. Hammond et al. (1995) reported sisters with GGT deficiency. The elder of the 2 sibs was detected during the course of a population screening on infants at

6 weeks of age using ascending paper chromatography of urine, which revealed a migration spot similar to that of cystine. Her growth and development were normal. During the second year, easy bruising was noted. Asthma was diagnosed at 2.5 years but was never a major problem. At 10 years of age, she began having attacks of absence and an EEG showed typical 3-Hz spike and wave activity.

Seizures were controlled by valproate medication. At age 21 years, she had no significant health problems, had a good secretarial position, and was pursuing a course at technical college. The younger sister was somewhat hypotonic and inactive at birth and had a dislocated hip and mild bilateral equinovarus. Tube feeding was required for the first 4 months. Problems noted later included strabismus, easy bruising, poor coordination, and some dysmorphic features. A diagnosis of Prader-Willi syndrome (PWS; 176270) was confirmed by demonstration of an interstitial deletion of 15q11-q13. Both sisters had normal red cell glutathione and no Heinz bodies. Clearly there were no specific clinical indicators for GGT deficiency, which in the younger sister was unrelated to PWS. Laperche et al.

(1986) cloned the structural gene for GGT from a rat kidney cDNA library. Taking advantage of its cross-

hybridization with the human genome, Bulle et al. (1987) mapped the GGT gene by in situ hybridization to 22q11.1–q11.2. A minor peak was found in 22q13.1. Rouleau et al. (1988) demonstrated a PvuII polymorphism at the GGT locus and added family linkage analysis to the methods by which GGT has been assigned to chromosome 22. From studies involving restriction analysis, Heisterkamp and Groffen (1988) presented evidence that the transcribed GGT gene lies 3–prime and just distal to the BCR locus (OMIM Ref. No. 151410). Rajpert–De Meyts et al. (1988) isolated cDNAs for GGT. Sakamuro et al. (1988) reported the primary structure of human GGT based on studies of a cDNA. The enzyme consists of 2 peptide chains, heavy and light, composed of 351 and 189 amino acids, respectively. Both are coded by a single gene; the 2 subunits of the mature enzyme are the products of processing of the single precursor peptide. The active site of GGT is located in the light subunit of the mature enzyme. A family of at least 4 GGT genes exists on chromosome 22 (Pawlak et al., 1988; Rajpert–De Meyts et al., 1988). At least 2 of these genes appear to be transcribed, since a human kidney cDNA has been isolated that differs from the placental and liver cDNAs (Pawlak et al., 1989).

[34343] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34344] Hammond, J. W.; Potter, M.; Wilcken, B.; Truscott, R. : Siblings with gamma-glutamyltransferase deficiency. J. Inherit. Metab. Dis. 18: 82–83, 1995. ; and

[34345] Rajpert-De Meyts, E.; Heisterkamp, N.; Groffen, J. : Cloning and nucleotide sequence of human gamma-glutamyl transpeptidase. Proc. Nat. Acad. Sci. 85: 8840–8844, 1988.

[34346] Further studies establishing the function and utilities of GGT1 are found in John Hopkins OMIM database record ID 231950, and in cited publications numbered 5775, 6382–6386, 3354–335 and 6387–6389 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Gamma-glutamyltransferase 2 (GGT2, Accession XM\_057166) is another VGAM908 host target gene. GGT2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by GGT2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GGT2 BINDING SITE, designated SEQ



ID:36487, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34347] Another function of VGAM908 is therefore inhibition of Gamma-glutamyltransferase 2 (GGT2, Accession XM\_057166). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GGT2. MHC Class II Transactivator (MHC2TA, Accession NM\_000246) is another VGAM908 host target gene. MHC2TA BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MHC2TA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MHC2TA BINDING SITE, designated SEQ ID:5777, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34348] Another function of VGAM908 is therefore inhibition of MHC Class II Transactivator (MHC2TA, Accession NM\_000246). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MHC2TA. Sialidase 3

(membrane sialidase) (NEU3, Accession NM\_006656) is another VGAM908 host target gene. NEU3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NEU3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NEU3 BINDING SITE, designated SEQ ID:13454, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34349] Another function of VGAM908 is therefore inhibition of Sialidase 3 (membrane sialidase) (NEU3, Accession NM\_006656). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NEU3. Asporin (LRR class 1) (ASPN, Accession NM\_017680) is another VGAM908 host target gene. ASPN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ASPN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASPN BINDING SITE, designated SEQ ID:19223, to the nucleotide sequence of VGAM908 RNA,

herein designated VGAM RNA, also designated SEQ ID:3619.

[34350] Another function of VGAM908 is therefore inhibition of Asporin (LRR class 1) (ASPN, Accession NM\_017680). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASPN. Chromosome 20 Open Reading Frame 110 (C20orf110, Accession XM\_086728) is another VGAM908 host target gene. C20orf110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C20orf110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C20orf110 BINDING SITE, designated SEQ ID:38834, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34351] Another function of VGAM908 is therefore inhibition of Chromosome 20 Open Reading Frame 110 (C20orf110, Accession XM\_086728). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C20orf110. DK-FZP566K023 (Accession NM\_015485) is another VGAM908

host target gene. DKFZP566K023 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP566K023, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566K023 BINDING SITE, designated SEQ ID:17756, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34352] Another function of VGAM908 is therefore inhibition of DKFZP566K023 (Accession NM\_015485). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566K023. F-box Only Protein 24 (FBXO24, Accession NM\_012172) is another VGAM908 host target gene. FBXO24 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FBXO24, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FBXO24 BINDING SITE, designated SEQ ID:14463, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ

ID:3619.

[34353] Another function of VGAM908 is therefore inhibition of F-box Only Protein 24 (FBXO24, Accession NM\_012172). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FBXO24. FLJ10956 (Accession NM\_018283) is another VGAM908 host target gene. FLJ10956 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10956, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10956 BINDING SITE, designated SEQ ID:20275, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34354] Another function of VGAM908 is therefore inhibition of FLJ10956 (Accession NM\_018283). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10956. FLJ20281 (Accession XM\_165663) is another VGAM908 host target gene. FLJ20281 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ20281, corresponding to a HOST TARGET

binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20281 BINDING SITE, designated SEQ ID:43724, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34355] Another function of VGAM908 is therefore inhibition of FLJ20281 (Accession XM\_165663). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20281. Integrin, Alpha 10 (ITGA10, Accession XM\_002097) is another VGAM908 host target gene. ITGA10 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ITGA10, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ITGA10 BINDING SITE, designated SEQ ID:29859, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34356] Another function of VGAM908 is therefore inhibition of Integrin, Alpha 10 (ITGA10, Accession XM\_002097). Accordingly, utilities of VGAM908 include diagnosis, preven-

tion and treatment of diseases and clinical conditions associated with ITGA10. KIAA0601 (Accession XM\_031267) is another VGAM908 host target gene. KIAA0601 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0601, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0601 BINDING SITE, designated SEQ ID:31328, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34357] Another function of VGAM908 is therefore inhibition of KIAA0601 (Accession XM\_031267). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0601. KIAA0700 (Accession XM\_050561) is another VGAM908 host target gene. KIAA0700 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA0700, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0700 BINDING SITE, designated SEQ ID:35657, to the

nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34358] Another function of VGAM908 is therefore inhibition of KIAA0700 (Accession XM\_050561). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0700. KIAA1373 (Accession XM\_048195) is another VGAM908 host target gene. KIAA1373 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1373, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1373 BINDING SITE, designated SEQ ID:35124, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34359] Another function of VGAM908 is therefore inhibition of KIAA1373 (Accession XM\_048195). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1373. KIAA1981 (Accession XM\_114000) is another VGAM908 host target gene. KIAA1981 BINDING SITE is HOST TARGET binding site found in the 3` untranslated



region of mRNA encoded by KIAA1981, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1981 BINDING SITE, designated SEQ ID:42607, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34360] Another function of VGAM908 is therefore inhibition of KIAA1981 (Accession XM\_114000). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1981. RNAC (Accession NM\_005772) is another VGAM908 host target gene. RNAC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNAC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNAC BINDING SITE, designated SEQ ID:12344, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34361] Another function of VGAM908 is therefore inhibition of RNAC (Accession NM\_005772). Accordingly, utilities of

VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNAC.

LOC129676 (Accession XM\_065341) is another VGAM908 host target gene. LOC129676 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC129676, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC129676 BINDING SITE, designated SEQ ID:37281, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34362] Another function of VGAM908 is therefore inhibition of LOC129676 (Accession XM\_065341). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC129676. LOC145678 (Accession XM\_096832) is another VGAM908 host target gene. LOC145678 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145678, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC145678 BINDING SITE, designated SEQ ID:40554, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34363] Another function of VGAM908 is therefore inhibition of LOC145678 (Accession XM\_096832). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145678. LOC152762 (Accession XM\_087518) is another VGAM908 host target gene. LOC152762 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152762, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152762 BINDING SITE, designated SEQ ID:39304, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34364] Another function of VGAM908 is therefore inhibition of LOC152762 (Accession XM\_087518). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152762. LOC199957 (Accession XM\_114068) is another VGAM908 host target gene. LOC199957 BINDING

SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC199957, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199957 BINDING SITE, designated SEQ ID:42673, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34365] Another function of VGAM908 is therefore inhibition of LOC199957 (Accession XM\_114068). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199957. LOC253024 (Accession XM\_174858) is another VGAM908 host target gene. LOC253024 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC253024, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253024 BINDING SITE, designated SEQ ID:46604, to the nucleotide sequence of VGAM908 RNA, herein designated VGAM RNA, also designated SEQ ID:3619.

[34366] Another function of VGAM908 is therefore inhibition of

LOC253024 (Accession XM\_174858). Accordingly, utilities of VGAM908 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253024. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 909 (VGAM909) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34367] VGAM909 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM909 was detected is described hereinabove with reference to Figs. 1–8.

[34368] VGAM909 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Alcelaphine Herpesvirus 1. VGAM909 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34369] VGAM909 gene encodes a VGAM909 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM909 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM909 precursor RNA is designated SEQ ID:895, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:895 is located at position 60240 relative to the genome of Alcelaphine Herpesvirus 1.

[34370] VGAM909 precursor RNA folds onto itself, forming VGAM909 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34371] An enzyme complex designated DICER COMPLEX, `dices` the VGAM909 folded precursor RNA into VGAM909 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide se-

quence of VGAM909 RNA is designated SEQ ID:3620, and is provided hereinbelow with reference to the sequence listing part.

[34372] VGAM909 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM909 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM909 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34373] VGAM909 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM909 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM909 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM909 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM909 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[34374] The complementary binding of VGAM909 RNA, herein designated VGAM RNA, to host target binding sites on VGAM909 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM909 host target RNA into VGAM909 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34375] It is appreciated that VGAM909 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM909 host target genes. The mRNA of each one of this plurality of VGAM909 host target genes comprises one or more host target binding sites, each



having a nucleotide sequence which is at least partly complementary to VGAM909 RNA, herein designated VGAM RNA, and which when bound by VGAM909 RNA causes inhibition of translation of respective one or more VGAM909 host target proteins.

[34376] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM909 gene, herein designated VGAM GENE, on one or more VGAM909 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34377] It is yet further appreciated that a function of VGAM909 is

inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of viral infection by Alcelaphine Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM909 correlate with, and may be deduced from, the identity of the host target genes which VGAM909 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34378] Nucleotide sequences of the VGAM909 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM909 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM909 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM909 are further described hereinbelow with reference to Table 1.

[34379] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM909 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM909 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34380] As mentioned hereinabove with reference to Fig. 1, a function of VGAM909 gene, herein designated VGAM is inhibition of expression of VGAM909 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM909 correlate with, and may be deduced from, the identity of the target genes which VGAM909 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34381] DNA Fragmentation Factor, 40kDa, Beta Polypeptide (caspase-activated DNase) (DFFB, Accession XM\_113366) is a VGAM909 host target gene. DFFB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DFFB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DFFB BINDING SITE, designated SEQ ID:42245, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34382] A function of VGAM909 is therefore inhibition of DNA Fragmentation Factor, 40kDa, Beta Polypeptide (caspase-activated DNase) (DFFB, Accession XM\_113366), a gene which induces DNA fragmentation and chromatin

condensation during apoptosis. Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DFFB. The function of DFFB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74. Desmocollin 2 (DSC2, Accession NM\_004949) is another VGAM909 host target gene. DSC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DSC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DSC2 BINDING SITE, designated SEQ ID:11392, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34383] Another function of VGAM909 is therefore inhibition of Desmocollin 2 (DSC2, Accession NM\_004949), a gene which is a component of intercellular desmosome junctions. Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DSC2. The function of DSC2 has been established by previous studies. Arnemann et al.

(1991) assigned the single gene responsible for DG II/III to the short arm of chromosome 9 by the study of somatic cell hybrids; however, King et al. (1993) cited unpublished data indicating that DSC3 is in fact not on 9p but rather on chromosome 18 where type 1 desmocollin (DSC1; 125643) is located. Tight linkage between the mouse homologs of NCAD (OMIM Ref. No. 114020), DSG1 (OMIM Ref. No. 125670), TTR (OMIM Ref. No. 176300), and DSC3, all of which are located in a region of mouse chromosome 18 with homology to human 18q, suggested that DSC3 was probably located on 18q12.1. Buxton et al. (1994) found that the human DSC3 gene maps to chromosome 18 by PCR amplification of DNA from a panel of rodent/human somatic cell hybrids. Greenwood et al. (1997) found that the human DSC2 gene, which codes for the most widely distributed form of desmocollins, contains 17 exons ranging in size from 46 to 258 bp and spans more than 32 kb of DNA. Exon 16 is alternatively spliced, giving rise to the a and b forms of the protein. A remarkable degree of conservation of intron position with other cadherins was observed.

[34384] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [34385] Arnemann, J.; Spurr, N. K.; Wheeler, G. N.; Parker, A. E.; Buxton, R. S. : Chromosomal assignment of the human genes coding for the major proteins of the desmosome junction, desmoglein DGI (DSG), desmocollins DGII/III (DSC), desmoplakins DPI/II (DSP), and plakoglobin DPIII (JUP). *Genomics* 10: 640–645, 1991. ; and
- [34386] Greenwood, M. D.; Marsden, M. D.; Cowley, C. M. E.; Sahota, V. K.; Buxton, R. S. : Exon–intron organization of the human type 2 desmocollin gene (DSC2): desmocollin gene structure is cl.
- [34387] Further studies establishing the function and utilities of DSC2 are found in John Hopkins OMIM database record ID 125645, and in cited publications numbered 361–36 and 359 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. EphB2 (EPHB2, Accession NM\_004442) is another VGAM909 host target gene. EPHB2 BINDING SITE1 and EPHB2 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by EPHB2, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of EPHB2 BINDING SITE1

and EPHB2 BINDING SITE2, designated SEQ ID:10735 and SEQ ID:18910 respectively, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34388] Another function of VGAM909 is therefore inhibition of EphB2 (EPHB2, Accession NM\_004442), a gene which Eph-related receptor tyrosine kinase B2; may have a role in neurogenesis. Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with EPHB2. The function of EPHB2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM533.JJAZ1 (Accession NM\_015355) is another VGAM909 host target gene. JJAZ1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by JJAZ1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of JJAZ1 BINDING SITE, designated SEQ ID:17657, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34389] Another function of VGAM909 is therefore inhibition of JJAZ1 (Accession NM\_015355), a gene which is a zinc finger protein. Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with JJAZ1. The function of JJAZ1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM231. Mitogen-activated Protein Kinase Kinase 1 (MAP2K1, Accession NM\_002755) is another VGAM909 host target gene. MAP2K1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MAP2K1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAP2K1 BINDING SITE, designated SEQ ID:8634, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34390] Another function of VGAM909 is therefore inhibition of Mitogen-activated Protein Kinase Kinase 1 (MAP2K1, Accession NM\_002755), a gene which is a signaling intermediate, may take part in cell transformation. Accordingly,



utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAP2K1. The function of MAP2K1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM528. N-ethylmaleimide-sensitive Factor Attachment Protein, Beta (NAPB, Accession XM\_046652) is another VGAM909 host target gene. NAPB BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NAPB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NAPB BINDING SITE, designated SEQ ID:34767, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34391] Another function of VGAM909 is therefore inhibition of N-ethylmaleimide-sensitive Factor Attachment Protein, Beta (NAPB, Accession XM\_046652). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NAPB. Retinoblastoma Binding Protein 9 (RBBP9, Accession XM\_046553) is another VGAM909 host target gene. RBBP9

BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RBBP9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RBBP9 BINDING SITE, designated SEQ ID:34742, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34392] Another function of VGAM909 is therefore inhibition of Retinoblastoma Binding Protein 9 (RBBP9, Accession XM\_046553). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RBBP9. Signal Transducer and Activator of Transcription 1, 91kDa (STAT1, Accession NM\_007315) is another VGAM909 host target gene. STAT1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by STAT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAT1 BINDING SITE, designated SEQ ID:14231, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ

ID:3620.

[34393] Another function of VGAM909 is therefore inhibition of Signal Transducer and Activator of Transcription 1, 91kDa (STAT1, Accession NM\_007315), a gene which is involved in transcriptional regulation. Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAT1. The function of STAT1 has been established by previous studies. STAT proteins have the dual function of signal transduction and activation of transcription (Darnell et al., 1994). These proteins are activated by phosphorylation on tyrosine in response to different ligands after which they form homodimers or heterodimers that translocate to the cell nucleus where they either directly bind to DNA or act together with other DNA-binding proteins in multiprotein transcription complexes to direct transcription. The first of these proteins to be described, which they termed STAT1 (for signal transduction and activator of transcription-1), is activated by a number of different ligands, including interferon-alpha (IFNA; 147660), interferon-gamma (IFNG; 147570), EGF (OMIM Ref. No. 131530), PDGF (see OMIM Ref. No. 173430), and IL6 (OMIM Ref. No. 147620). The same tyrosine residue is activated at least

by IFN- $\alpha$ , IFN- $\gamma$ , and EGF. STAT2 (OMIM Ref. No. 600556), in contrast, is activated by IFN- $\alpha$  but not by IFN- $\gamma$  or any of the other ligands mentioned above. STAT3 is known to be activated by IGF, IL6, LIF, and perhaps other ligands but is not activated by IFN- $\gamma$ . STAT4 (OMIM Ref. No. 600558) is present in high concentration in the testis but has not been found in a phosphorylated form in cells. The STAT proteins differ in the DNA sites to which they bind. STAT1 homodimer binds to a site termed GAS, first defined as required for IFN- $\gamma$  induction. Variations on this site are also used in response to IL6, PDGF, and other ligands. Animal model experiments lend further support to the function of STAT1. Meraz et al. (1996) reported the generation and characterization of mice deficient in Stat1. Stat1-deficient mice showed no overt development abnormalities but displayed a complete lack of responsiveness to either interferon- $\alpha$  or interferon- $\gamma$  and were highly sensitive to infection by microbial pathogens and viruses. In contrast, these mice responded normally to several other cytokines that activate Stat1 in vitro. These observations documented that STAT1 plays an obligate and dedicated role in mediating IFN-dependent biologic responses and revealed

an unexpected level of physiologic specificity for STAT1 action.

[34394] It is appreciated that the abovementioned animal model for STAT1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[34395] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34396] Darnell, J. E., Jr.; Kerr, I. M.; Stark, G. M. : Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science 264: 1415-1421, 1994. ; and

[34397] Meraz, M. A.; White, J. M.; Sheehan, K. C. F.; Bach, E. A.; Rodig, S. J.; Dighe, A. S.; Kaplan, D. H.; Riley, J. K.; Greenlund, A. C. Campbell, D.; Carver-Moore, K.; DuBois, R. N.; Clar.

[34398] Further studies establishing the function and utilities of STAT1 are found in John Hopkins OMIM database record ID 600555, and in cited publications numbered 8095-8097, 6079, 8098-8100, 11676, 12053-8103, 168 and 12330 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. TIM3

(Accession NM\_032782) is another VGAM909 host target gene. TIM3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TIM3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TIM3 BINDING SITE, designated SEQ ID:26524, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34399] Another function of VGAM909 is therefore inhibition of TIM3 (Accession NM\_032782), a gene which regulates macrophage activation and enhances the severity of experimental autoimmune encephalomyelitis in mice. Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TIM3. The function of TIM3 has been established by previous studies. By immunoscreening Th1 and Th2 cells with monoclonal antibodies derived from mouse Th1 cell-immunized rats, followed by gene-expression cloning, Monney et al. (2002) obtained a cDNA encoding mouse Tim3. By genomic database searching and RT-PCR, the authors isolated a cDNA encoding human TIM3. The deduced 301-amino acid type I membrane protein, 63%

identical overall and 77% identical in the cytoplasmic domain, has an Ig variable-like domain, a mucin-like domain consisting of 31% serine and threonine residues, and a cytoplasmic domain with a tyrosine phosphorylation motif. Monney et al. (2002) noted that TIM3 is related to the hepatitis A virus cellular receptor (HAVCR1; 606518), also known as the kidney injury molecule (Kim1). Using flow cytometric and RT-PCR analysis, Monney et al. (2002) detected Tim3 only on activated Th1 cells and CD11b+ (ITGAM; 120980) macrophages. Cells expressing Tim3 predominate in the central nervous system of mice at the onset of experimental autoimmune encephalomyelitis (EAE), a Th1-mediated autoimmune disease. Anti-Tim3 treatment enhanced the clinical and pathologic severity of EAE and increased the number and activation level of macrophages. Monney et al. (2002) proposed that anti-Tim3 may trigger the production of proinflammatory cytokines in vivo and induce macrophage activation possibly by enhancing the migration of Th1 cells into the brain or by blocking an interaction between Tim3 and an inhibitory ligand.

[34400] Full details of the abovementioned studies are described in the following publications, the disclosure of which are

hereby incorporated by reference:

- [34401] Monney, L.; Sabatos, C.; Gaglia, J. L.; Ryu, A.; Waldner, H.; Chernova, T.; Manning, S.; Greenfield, E. A.; Coyle, A. J.; Sobel, R. A.; Freeman, G. J.; Kuchroo, V. K. : Th1-specific cell surface protein regulates macrophage activation and severity of an autoimmune disease. *Nature* 415: 536–541, 2002. ; and
- [34402] McIntire, J. J.; Umetsu, S. E.; Akbari, O.; Potter, M.; Kuchroo, V. K.; Barsh, G. S.; Freeman, G. J.; Umetsu, D. T.; DeKruyff, R. H. : Identification of Tapr (an airway hyperre-activity.
- [34403] Further studies establishing the function and utilities of TIM3 are found in John Hopkins OMIM database record ID 606652, and in cited publications numbered 6839 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Bifunctional Apoptosis Regulator (BFAR, Accession XM\_027311) is another VGAM909 host target gene. BFAR BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by BFAR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BFAR BINDING SITE,



designated SEQ ID:30478, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34404] Another function of VGAM909 is therefore inhibition of Bifunctional Apoptosis Regulator (BFAR, Accession XM\_027311). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BFAR. CMRF-35H (Accession XM\_046925) is another VGAM909 host target gene. CMRF-35H BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CMRF-35H, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CMRF-35H BINDING SITE, designated SEQ ID:34862, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34405] Another function of VGAM909 is therefore inhibition of CMRF-35H (Accession XM\_046925). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CMRF-35H. Cleavage and Polyadenylation Specific Factor 2,

100kDa (CPSF2, Accession XM\_029311) is another VGAM909 host target gene. CPSF2 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by CPSF2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CPSF2 BINDING SITE, designated SEQ ID:30863, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34406] Another function of VGAM909 is therefore inhibition of Cleavage and Polyadenylation Specific Factor 2, 100kDa (CPSF2, Accession XM\_029311). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CPSF2. DKFZP564D0764 (Accession XM\_113964) is another VGAM909 host target gene. DKFZP564D0764 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP564D0764, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP564D0764 BINDING SITE, designated

SEQ ID:42574, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34407] Another function of VGAM909 is therefore inhibition of DKFZP564D0764 (Accession XM\_113964). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP564D0764. FLJ10697 (Accession NM\_018181) is another VGAM909 host target gene. FLJ10697 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10697, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10697 BINDING SITE, designated SEQ ID:20016, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34408] Another function of VGAM909 is therefore inhibition of FLJ10697 (Accession NM\_018181). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10697. FLJ10704 (Accession NM\_018185) is another VGAM909 host target gene. FLJ10704 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ10704, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10704 BINDING SITE, designated SEQ ID:20030, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34409] Another function of VGAM909 is therefore inhibition of FLJ10704 (Accession NM\_018185). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10704. FLJ11722 (Accession NM\_024970) is another VGAM909 host target gene. FLJ11722 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ11722, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11722 BINDING SITE, designated SEQ ID:24521, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34410] Another function of VGAM909 is therefore inhibition of

FLJ11722 (Accession NM\_024970). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11722. KIAA0335 (Accession NM\_014803) is another VGAM909 host target gene. KIAA0335 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0335, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0335 BINDING SITE, designated SEQ ID:16734, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34411] Another function of VGAM909 is therefore inhibition of KIAA0335 (Accession NM\_014803). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0335. KIAA0976 (Accession NM\_014917) is another VGAM909 host target gene. KIAA0976 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0976, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA0976 BINDING SITE, designated SEQ ID:17162, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34412] Another function of VGAM909 is therefore inhibition of KIAA0976 (Accession NM\_014917). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0976. KIAA1727 (Accession XM\_034262) is another VGAM909 host target gene. KIAA1727 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1727, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1727 BINDING SITE, designated SEQ ID:32031, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34413] Another function of VGAM909 is therefore inhibition of KIAA1727 (Accession XM\_034262). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1727. KIAA1938 (Accession XM\_166407) is another

VGAM909 host target gene. KIAA1938 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1938, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1938 BINDING SITE, designated SEQ ID:44279, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34414] Another function of VGAM909 is therefore inhibition of KIAA1938 (Accession XM\_166407). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1938. SEC15L (Accession XM\_051147) is another VGAM909 host target gene. SEC15L BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SEC15L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEC15L BINDING SITE, designated SEQ ID:35765, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34415] Another function of VGAM909 is therefore inhibition of SEC15L (Accession XM\_051147). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEC15L. TSPAN-2 (Accession NM\_005725) is another VGAM909 host target gene. TSPAN-2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TSPAN-2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TSPAN-2 BINDING SITE, designated SEQ ID:12278, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34416] Another function of VGAM909 is therefore inhibition of TSPAN-2 (Accession NM\_005725). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TSPAN-2. Zinc Finger Protein 297B (ZNF297B, Accession NM\_014007) is another VGAM909 host target gene. ZNF297B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ZNF297B, corresponding to a HOST TARGET binding site



such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF297B BINDING SITE, designated SEQ ID:15220, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34417] Another function of VGAM909 is therefore inhibition of Zinc Finger Protein 297B (ZNF297B, Accession NM\_014007). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF297B. LOC143879 (Accession XM\_084666) is another VGAM909 host target gene. LOC143879 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC143879, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143879 BINDING SITE, designated SEQ ID:37659, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34418] Another function of VGAM909 is therefore inhibition of LOC143879 (Accession XM\_084666). Accordingly, utilities

of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143879. LOC151057 (Accession XM\_097998) is another VGAM909 host target gene. LOC151057 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC151057, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151057 BINDING SITE, designated SEQ ID:41294, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34419] Another function of VGAM909 is therefore inhibition of LOC151057 (Accession XM\_097998). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151057. LOC199957 (Accession XM\_114068) is another VGAM909 host target gene. LOC199957 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC199957, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC199957 BINDING SITE, designated SEQ ID:42674, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34420] Another function of VGAM909 is therefore inhibition of LOC199957 (Accession XM\_114068). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199957. LOC202934 (Accession XM\_117486) is another VGAM909 host target gene. LOC202934 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202934, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202934 BINDING SITE, designated SEQ ID:43460, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34421] Another function of VGAM909 is therefore inhibition of LOC202934 (Accession XM\_117486). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202934. LOC253612 (Accession XM\_172985) is another VGAM909 host target gene. LOC253612 BINDING

SITE is HOST TARGET binding site found in the 3` un-translated region of mRNA encoded by LOC253612, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC253612 BINDING SITE, designated SEQ ID:46255, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34422] Another function of VGAM909 is therefore inhibition of LOC253612 (Accession XM\_172985). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC253612. LOC257017 (Accession XM\_173227) is another VGAM909 host target gene. LOC257017 BINDING SITE is HOST TARGET binding site found in the 5` un-translated region of mRNA encoded by LOC257017, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257017 BINDING SITE, designated SEQ ID:46491, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34423] Another function of VGAM909 is therefore inhibition of

LOC257017 (Accession XM\_173227). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257017. LOC92573 (Accession XM\_045884) is another VGAM909 host target gene. LOC92573 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92573, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92573 BINDING SITE, designated SEQ ID:34599, to the nucleotide sequence of VGAM909 RNA, herein designated VGAM RNA, also designated SEQ ID:3620.

[34424] Another function of VGAM909 is therefore inhibition of LOC92573 (Accession XM\_045884). Accordingly, utilities of VGAM909 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92573. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 910 (VGAM910) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[34425] VGAM910 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM910 was detected is described hereinabove with reference to Figs. 1–8.

[34426] VGAM910 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Alcelaphine Herpesvirus 1. VGAM910 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34427] VGAM910 gene encodes a VGAM910 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM910 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM910 precursor RNA is designated SEQ ID:896, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:896 is located at position 61092 relative to the genome of Alcelaphine Herpesvirus 1.

[34428] VGAM910 precursor RNA folds onto itself, forming VGAM910 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[34429] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM910 folded precursor RNA into VGAM910 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 70%) nucleotide se-  
quence of VGAM910 RNA is designated SEQ ID:3621, and  
is provided hereinbelow with reference to the sequence  
listing part.

[34430] VGAM910 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM910 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM910 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[34431] VGAM910 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM910 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM910 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM910 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM910 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR



and 5`UTR regions.

[34432] The complementary binding of VGAM910 RNA, herein designated VGAM RNA, to host target binding sites on VGAM910 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM910 host target RNA into VGAM910 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34433] It is appreciated that VGAM910 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM910 host target genes. The mRNA of each one of this plurality of VGAM910 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM910 RNA, herein designated VGAM RNA, and which when bound by VGAM910 RNA causes inhibition of translation of respective one or more VGAM910 host target proteins.

[34434] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM910 gene, herein designated VGAM GENE, on one or

more VGAM910 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34435] It is yet further appreciated that a function of VGAM910 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of viral infection by Alcelaphine Herpesvirus 1. Specific functions, and accordingly utilities, of VGAM910 correlate with, and may be deduced from, the identity of the host target genes which VGAM910 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [34436] Nucleotide sequences of the VGAM910 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM910 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM910 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM910 are further described hereinbelow with reference to Table 1.
- [34437] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM910 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM910 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [34438] As mentioned hereinabove with reference to Fig. 1, a function of VGAM910 gene, herein designated VGAM is inhibition of expression of VGAM910 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM910 correlate with, and may be deduced from, the identity of the target genes which VGAM910 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [34439] Bone Morphogenetic Protein 4 (BMP4, Accession

NM\_001202) is a VGAM910 host target gene. BMP4 BINDING SITE1 through BMP4 BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by BMP4, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BMP4 BINDING SITE1 through BMP4 BINDING SITE3, designated SEQ ID:6867, SEQ ID:28388 and SEQ ID:28389 respectively, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34440] A function of VGAM910 is therefore inhibition of Bone Morphogenetic Protein 4 (BMP4, Accession NM\_001202), a gene which acts in mesoderm induction, tooth development, limb formation and fracture repair. Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BMP4. The function of BMP4 has been established by previous studies. Shafritz et al. (1996) found overexpression of BMP4 in lymphoblastoid cell lines from 26 of 32 patients with fibrodysplasia ossificans progressiva (FOP; 135100), but from only 1 of 12 normal subjects (P less than 0.001). Furthermore, BMP4 and its mRNA were de-

tected in the lymphoblastoid cell lines from a man with FOP and his 3 affected children, but not from the children's unaffected mother. Cosegregation of DNA markers for the BMP4 locus on chromosome 14 in the rare families in which FOP is inherited would strengthen the candidacy of BMP4, and the demonstration of mutations in the BMP4 gene, especially in the promoter sequences, would be confirmatory. Animal model experiments lend further support to the function of BMP4. Connor (1996) speculated that transgenic mice with selective overexpression of BMP4 may serve as animal models of FOP and may make it possible to evaluate potential therapies directed at influencing the expression of BMP4 or its 2 types of cell-surface receptors. Not only may this knowledge provide a rational basis for therapy for FOP, but possibly also measures for the control of local ectopic bone development which occurs in 10 to 20% of patients who have undergone surgical hip replacement. According to Connor (1996), there appears to be an individual propensity to the phenomenon of secondary ectopic ossification of soft tissue. In the 10 to 20% of patients who develop local ectopic bone formation after hip replacement, if surgical removal of that bone is attempted or the opposite hip is re-

placed, ectopic bone almost invariably recurs or occurs.

[34441] It is appreciated that the abovementioned animal model for BMP4 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[34442] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34443] Shafritz, A. B.; Shore, E. M.; Gannon, F. H.; Zasloff, M. A.; Taub, R.; Muenke, M.; Kaplan, F. S. : Overexpression of an osteogenic morphogen in fibrodysplasia ossificans progressiva. New Eng. J. Med. 335: 555–561, 1996. ; and

[34444] Connor, J. M. : Fibrodysplasia ossificans progressiva: lessons from rare maladies. (Editorial) New Eng. J. Med. 335: 591–593, 1996.

[34445] Further studies establishing the function and utilities of BMP4 are found in John Hopkins OMIM database record ID 112262, and in cited publications numbered 1163 and 11632–11639 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Coagulation Factor VIII, Procoagulant Component (hemophilia A) (F8, Accession NM\_000132) is another VGAM910 host target gene. F8 BINDING SITE is HOST

TARGET binding site found in the 3` untranslated region of mRNA encoded by F8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of F8 BINDING SITE, designated SEQ ID:5616, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34446] Another function of VGAM910 is therefore inhibition of Coagulation Factor VIII, Procoagulant Component (hemophilia A) (F8, Accession NM\_000132). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with F8. Interleukin 2 Receptor, Beta (IL2RB, Accession NM\_000878) is another VGAM910 host target gene. IL2RB BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by IL2RB, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL2RB BINDING SITE, designated SEQ ID:6573, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34447] Another function of VGAM910 is therefore inhibition of Interleukin 2 Receptor, Beta (IL2RB, Accession NM\_000878), a gene which is involved in receptor mediated endocytosis and transduces the mitogenic signals of il-2. Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL2RB. The function of IL2RB and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM450. Keratin, Hair, Acidic, 8 (KRTHA8, Accession NM\_006771) is another VGAM910 host target gene. KRTHA8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KRTHA8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KRTHA8 BINDING SITE, designated SEQ ID:13644, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34448] Another function of VGAM910 is therefore inhibition of Keratin, Hair, Acidic, 8 (KRTHA8, Accession NM\_006771), a gene which is a type I keratin that may form intermediate



filaments. Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KRTHA8. The function of KRTHA8 has been established by previous studies. Rogers et al. (1998) isolated and characterized 2 overlapping human PAC clones that cover 190 kb on 17q12–q21. These clones contain 9 type I hair keratin genes, including the novel genes KRTHA7 (OMIM Ref. No. 604541) and KRTHA8; 1 transcribed hair keratin pseudogene; and 1 orphan exon. The order of the genes is 5–prime--KRTHA6 (OMIM Ref. No. 604540)--KRTHA5 (OMIM Ref. No. 602764)--KRTHA2 (OMIM Ref. No. 602760)--orphan exon--KRTHA8--KRTHA7--pseudogene--KRTHA1--KRTHA4 (OMIM Ref. No. 602763)--KRTHA3B (OMIM Ref. No. 602762)--KRTHA3A (OMIM Ref. No. 602761)--3–prime. The hair keratin genes range in size from 4.2 to 7.5 kb, and the genes are separated from each other by 5.5 to 18.4 kb; all are located within about 140 kb. Each gene is transcribed from the 5–prime to 3–prime direction. Based on sequence homologies, the genes can be grouped into 3 subclusters of tandemly arranged genes. One subcluster, group A, consists of KRTHA1, KRTHA3A, KRTHA3B, and

KRTHA4, which share 89% overall amino acid identity. A second subcluster, group B, contains KRTHA7 and KRTHA8, as well as the hair keratin pseudogene, which the authors called HAA. The functional hair keratins and hypothetical HAA hair keratin share approximately 81% overall amino acid identity. Due to an almost completely identical head domain, KRTHA7 and KRTHA8 are 92.6% identical. The third subcluster, group C, consists of the structurally less related hair keratins KRTHA2, KRTHA5, and KRTHA6, which share about 70% amino acid identity. Rogers et al. (1998) found that the deduced KRTHA8 protein, which they called HA8, has 415 amino acids. The KRTHA8 gene contains 7 exons. By RT-PCR, Rogers et al. (1998) showed that KRTHA8 is expressed in the human hair follicle. See Langbein et al. (1999) for further details on the expression pattern of the KRTHA8 gene in the hair follicle.

[34449] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34450] Langbein, L.; Rogers, M. A.; Winter, H.; Silke, P.; Beckhaus, U.; Rackwitz, H.-R.; Schweizer, J. : The catalog of human hair keratins. I. Expression of the nine type I members in

the hair follicle. J. Biol. Chem. 274: 19874–19884, 1999. ;  
and

[34451] Rogers, M. A.; Winter, H.; Wolf, C.; Heck, M.; Schweizer, J. :  
Characterization of a 190–kilobase pair domain of human  
type I hair keratin genes. J. Biol. Chem. 273:  
26683–26691, 1998.

[34452] Further studies establishing the function and utilities of  
KRTHA8 are found in John Hopkins OMIM database record  
ID 604542, and in cited publications numbered  
1257–1258 listed in the bibliography section hereinbelow,  
which are also hereby incorporated by refer-  
ence. Mesenchyme Homeo Box 2 (growth arrest–specific  
homeo box) (MEOX2, Accession NM\_005924) is another  
VGAM910 host target gene. MEOX2 BINDING SITE is HOST  
TARGET binding site found in the 3` untranslated region  
of mRNA encoded by MEOX2, corresponding to a HOST  
TARGET binding site such as BINDING SITE I, BINDING SITE  
II or BINDING SITE III. Table 2 illustrates the complemen-  
tarity of the nucleotide sequences of MEOX2 BINDING  
SITE, designated SEQ ID:12548, to the nucleotide se-  
quence of VGAM910 RNA, herein designated VGAM RNA,  
also designated SEQ ID:3621.

[34453] Another function of VGAM910 is therefore inhibition of

Mesenchyme Homeo Box 2 (growth arrest-specific homeo box) (MEOX2, Accession NM\_005924), a gene which roles in mesoderm induction and, somitogenesis, and myogenic and sclerotomal differentiation. Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MEOX2. The function of MEOX2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM827. Nitric Oxide Synthase 1 (neuronal) (NOS1, Accession NM\_000620) is another VGAM910 host target gene. NOS1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NOS1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NOS1 BINDING SITE, designated SEQ ID:6228, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34454] Another function of VGAM910 is therefore inhibition of Nitric Oxide Synthase 1 (neuronal) (NOS1, Accession NM\_000620), a gene which produces nitric oxide (no) which is a messenger molecule with diverse functions

throughout the body. Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NOS1. The function of NOS1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM323. Protein Kinase C and Casein Kinase Substrate In Neurons 1 (PACSIN1, Accession XM\_166424) is another VGAM910 host target gene. PACSIN1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PACSIN1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PACSIN1 BINDING SITE, designated SEQ ID:44318, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34455] Another function of VGAM910 is therefore inhibition of Protein Kinase C and Casein Kinase Substrate In Neurons 1 (PACSIN1, Accession XM\_166424). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PACSIN1. Sclerosteosis (SOST, Accession NM\_025237) is another

VGAM910 host target gene. SOST BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SOST, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SOST BINDING SITE, designated SEQ ID:24918, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34456] Another function of VGAM910 is therefore inhibition of Sclerosteosis (SOST, Accession NM\_025237). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SOST. Angiomotin (AMOT, Accession NM\_133265) is another VGAM910 host target gene. AMOT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AMOT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AMOT BINDING SITE, designated SEQ ID:28414, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34457] Another function of VGAM910 is therefore inhibition of Angiomotin (AMOT, Accession NM\_133265). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AMOT. Adaptor-related Protein Complex 4, Sigma 1 Subunit (AP4S1, Accession NM\_007077) is another VGAM910 host target gene. AP4S1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by AP4S1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AP4S1 BINDING SITE, designated SEQ ID:13942, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34458] Another function of VGAM910 is therefore inhibition of Adaptor-related Protein Complex 4, Sigma 1 Subunit (AP4S1, Accession NM\_007077). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AP4S1. DKFZP434N161 (Accession XM\_085920) is another VGAM910 host target gene. DKFZP434N161 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by DKFZP434N161, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434N161 BINDING SITE, designated SEQ ID:38396, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34459] Another function of VGAM910 is therefore inhibition of DKFZP434N161 (Accession XM\_085920). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP434N161. FLJ11004 (Accession NM\_018296) is another VGAM910 host target gene. FLJ11004 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ11004, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11004 BINDING SITE, designated SEQ ID:20285, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34460] Another function of VGAM910 is therefore inhibition of FLJ11004 (Accession NM\_018296). Accordingly, utilities of



VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11004. FLJ11560 (Accession NM\_025182) is another VGAM910 host target gene. FLJ11560 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by FLJ11560, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11560 BINDING SITE, designated SEQ ID:24819, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34461] Another function of VGAM910 is therefore inhibition of FLJ11560 (Accession NM\_025182). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11560. FLJ13263 (Accession NM\_025125) is another VGAM910 host target gene. FLJ13263 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13263, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13263 BINDING SITE,

designated SEQ ID:24768, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34462] Another function of VGAM910 is therefore inhibition of FLJ13263 (Accession NM\_025125). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13263. IMPACT (Accession NM\_018439) is another VGAM910 host target gene. IMPACT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IMPACT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IMPACT BINDING SITE, designated SEQ ID:20503, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34463] Another function of VGAM910 is therefore inhibition of IMPACT (Accession NM\_018439). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IMPACT. KIAA1157 (Accession XM\_051093) is another VGAM910 host target gene. KIAA1157 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by KIAA1157, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1157 BINDING SITE, designated SEQ ID:35750, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34464] Another function of VGAM910 is therefore inhibition of KIAA1157 (Accession XM\_051093). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1157. KIAA1170 (Accession XM\_045907) is another VGAM910 host target gene. KIAA1170 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1170 BINDING SITE, designated SEQ ID:34610, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34465] Another function of VGAM910 is therefore inhibition of

KIAA1170 (Accession XM\_045907). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1170. KIAA1276 (Accession XM\_039169) is another VGAM910 host target gene. KIAA1276 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KIAA1276, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1276 BINDING SITE, designated SEQ ID:33018, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34466] Another function of VGAM910 is therefore inhibition of KIAA1276 (Accession XM\_039169). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1276. KIAA1937 (Accession XM\_057107) is another VGAM910 host target gene. KIAA1937 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1937, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the

complementarity of the nucleotide sequences of KIAA1937 BINDING SITE, designated SEQ ID:36484, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34467] Another function of VGAM910 is therefore inhibition of KIAA1937 (Accession XM\_057107). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1937. LCE (Accession NM\_024090) is another VGAM910 host target gene. LCE BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LCE, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LCE BINDING SITE, designated SEQ ID:23534, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34468] Another function of VGAM910 is therefore inhibition of LCE (Accession NM\_024090). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LCE. MAD4 (Accession NM\_006454) is another VGAM910 host

target gene. MAD4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MAD4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MAD4 BINDING SITE, designated SEQ ID:13168, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34469] Another function of VGAM910 is therefore inhibition of MAD4 (Accession NM\_006454). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MAD4. RAS Guanyl Releasing Protein 4 (RASGRP4, Accession NM\_052949) is another VGAM910 host target gene. RAS-GRP4 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by RASGRP4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RASGRP4 BINDING SITE, designated SEQ ID:27503, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ

ID:3621.

[34470] Another function of VGAM910 is therefore inhibition of RAS Guanyl Releasing Protein 4 (RASGRP4, Accession NM\_052949). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RASGRP4. LOC127262 (Accession XM\_072073) is another VGAM910 host target gene. LOC127262 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC127262, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC127262 BINDING SITE, designated SEQ ID:37458, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34471] Another function of VGAM910 is therefore inhibition of LOC127262 (Accession XM\_072073). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC127262. LOC137075 (Accession XM\_059895) is another VGAM910 host target gene. LOC137075 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC137075, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC137075 BINDING SITE, designated SEQ ID:37103, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34472] Another function of VGAM910 is therefore inhibition of LOC137075 (Accession XM\_059895). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC137075. LOC153688 (Accession XM\_098416) is another VGAM910 host target gene. LOC153688 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153688, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153688 BINDING SITE, designated SEQ ID:41655, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34473] Another function of VGAM910 is therefore inhibition of LOC153688 (Accession XM\_098416). Accordingly, utilities



of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153688. LOC158972 (Accession XM\_099009) is another VGAM910 host target gene. LOC158972 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC158972, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158972 BINDING SITE, designated SEQ ID:42042, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34474] Another function of VGAM910 is therefore inhibition of LOC158972 (Accession XM\_099009). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158972. LOC196540 (Accession XM\_116933) is another VGAM910 host target gene. LOC196540 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC196540, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC196540 BINDING SITE, designated SEQ ID:43151, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34475] Another function of VGAM910 is therefore inhibition of LOC196540 (Accession XM\_116933). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196540. LOC221832 (Accession XM\_166496) is another VGAM910 host target gene. LOC221832 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC221832, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC221832 BINDING SITE, designated SEQ ID:44426, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34476] Another function of VGAM910 is therefore inhibition of LOC221832 (Accession XM\_166496). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC221832. LOC255465 (Accession XM\_173206) is another VGAM910 host target gene. LOC255465 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC255465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC255465 BINDING SITE, designated SEQ ID:46453, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34477] Another function of VGAM910 is therefore inhibition of LOC255465 (Accession XM\_173206). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC255465. LOC57109 (Accession NM\_020385) is another VGAM910 host target gene. LOC57109 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC57109, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC57109 BINDING SITE, designated SEQ ID:21655, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34478] Another function of VGAM910 is therefore inhibition of

LOC57109 (Accession NM\_020385). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC57109. LOC90538 (Accession XM\_032401) is another VGAM910 host target gene. LOC90538 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC90538, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90538 BINDING SITE, designated SEQ ID:31656, to the nucleotide sequence of VGAM910 RNA, herein designated VGAM RNA, also designated SEQ ID:3621.

[34479] Another function of VGAM910 is therefore inhibition of LOC90538 (Accession XM\_032401). Accordingly, utilities of VGAM910 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90538. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 911 (VGAM911) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is

known in the art.

[34480] VGAM911 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM911 was detected is described hereinabove with reference to Figs. 1–8.

[34481] VGAM911 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 8. VGAM911 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34482] VGAM911 gene encodes a VGAM911 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM911 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM911 precursor RNA is designated SEQ ID:897, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:897 is located at position 56711 relative to the genome of Human Herpesvirus 8.

[34483] VGAM911 precursor RNA folds onto itself, forming VGAM911 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional

`hairpin structure`. As is well known in the art, this  
`hairpin structure`, is typical of RNA encoded by miRNA  
genes, and is due to the fact that the nucleotide sequence  
of the first half of the RNA encoded by a miRNA gene is an  
accurate or partial inversed-reversed sequence of the nu-  
cleotide sequence of the second half thereof.

[34484] An enzyme complex designated DICER COMPLEX, `dices`  
the VGAM911 folded precursor RNA into VGAM911 RNA,  
herein designated VGAM RNA, a single stranded ~22 nt  
long RNA segment. As is known in the art, `dicing` of a  
hairpin structured RNA precursor product into a short  
~22nt RNA segment is catalyzed by an enzyme complex  
comprising an enzyme called Dicer together with other  
necessary proteins. A probable (over 81%) nucleotide se-  
quence of VGAM911 RNA is designated SEQ ID:3622, and  
is provided hereinbelow with reference to the sequence  
listing part.

[34485] VGAM911 host target gene, herein designated VGAM  
HOST TARGET GENE, encodes a corresponding messenger  
RNA, VGAM911 host target RNA, herein designated VGAM  
HOST TARGET RNA. VGAM911 host target RNA comprises  
three regions, as is typical of mRNA of a protein coding  
gene: a 5` untranslated region, a protein coding region

and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[34486] VGAM911 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM911 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM911 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM911 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM911 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR

and 5`UTR regions.

[34487] The complementary binding of VGAM911 RNA, herein designated VGAM RNA, to host target binding sites on VGAM911 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM911 host target RNA into VGAM911 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34488] It is appreciated that VGAM911 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM911 host target genes. The mRNA of each one of this plurality of VGAM911 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM911 RNA, herein designated VGAM RNA, and which when bound by VGAM911 RNA causes inhibition of translation of respective one or more VGAM911 host target proteins.

[34489] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM911 gene, herein designated VGAM GENE, on one or



more VGAM911 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34490] It is yet further appreciated that a function of VGAM911 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 8. Specific functions, and accordingly utilities, of VGAM911 correlate with, and may be deduced from, the identity of the host target genes which VGAM911 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [34491] Nucleotide sequences of the VGAM911 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM911 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM911 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM911 are further described hereinbelow with reference to Table 1.
- [34492] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM911 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM911 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [34493] As mentioned hereinabove with reference to Fig. 1, a function of VGAM911 gene, herein designated VGAM is inhibition of expression of VGAM911 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM911 correlate with, and may be deduced from, the identity of the target genes which VGAM911 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.
- [34494] Cadherin 1, Type 1, E-cadherin (epithelial) (CDH1, Acces-

sion NM\_004360) is a VGAM911 host target gene. CDH1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CDH1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CDH1 BINDING SITE, designated SEQ ID:10562, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34495] A function of VGAM911 is therefore inhibition of Cadherin 1, Type 1, E-cadherin (epithelial) (CDH1, Accession NM\_004360). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CDH1. N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243) is another VGAM911 host target gene. NDRG1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by NDRG1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDRG1 BINDING SITE, designated SEQ ID:29967, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA,

also designated SEQ ID:3622.

[34496] Another function of VGAM911 is therefore inhibition of N-myc Downstream Regulated Gene 1 (NDRG1, Accession XM\_005243), a gene which may have a growth inhibitory role. Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDRG1. The function of NDRG1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM144.Syntrophin, Beta 1 (dystrophin-associated protein A1, 59kDa, basic component 1) (SNTB1, Accession NM\_021021) is another VGAM911 host target gene. SNTB1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SNTB1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SNTB1 BINDING SITE, designated SEQ ID:22012, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34497] Another function of VGAM911 is therefore inhibition of

Syntrophin, Beta 1 (dystrophin-associated protein A1, 59kDa, basic component 1) (SNTB1, Accession NM\_021021). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SNTB1. Zinc Finger Protein 138 (clone pHZ-32) (ZNF138, Accession XM\_088081) is another VGAM911 host target gene. ZNF138 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ZNF138, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZNF138 BINDING SITE, designated SEQ ID:39508, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34498] Another function of VGAM911 is therefore inhibition of Zinc Finger Protein 138 (clone pHZ-32) (ZNF138, Accession XM\_088081). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZNF138. AOP2 (Accession NM\_004905) is another VGAM911 host target gene. AOP2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by

AOP2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AOP2 BINDING SITE, designated SEQ ID:11341, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34499] Another function of VGAM911 is therefore inhibition of AOP2 (Accession NM\_004905). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AOP2. BCL2-like 12 (proline rich) (BCL2L12, Accession NM\_138639) is another VGAM911 host target gene. BCL2L12 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by BCL2L12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL2L12 BINDING SITE, designated SEQ ID:28915, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34500] Another function of VGAM911 is therefore inhibition of BCL2-like 12 (proline rich) (BCL2L12, Accession

NM\_138639). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL2L12. FLJ14129 (Accession NM\_030895) is another VGAM911 host target gene. FLJ14129 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14129, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14129 BINDING SITE, designated SEQ ID:25164, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34501] Another function of VGAM911 is therefore inhibition of FLJ14129 (Accession NM\_030895). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14129. HSPC043 (Accession XM\_041943) is another VGAM911 host target gene. HSPC043 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPC043, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of HSPC043 BINDING SITE, designated SEQ ID:33637, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34502] Another function of VGAM911 is therefore inhibition of HSPC043 (Accession XM\_041943). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HSPC043. LOC199796 (Accession XM\_058994) is another VGAM911 host target gene. LOC199796 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC199796, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC199796 BINDING SITE, designated SEQ ID:36810, to the nucleotide sequence of VGAM911 RNA, herein designated VGAM RNA, also designated SEQ ID:3622.

[34503] Another function of VGAM911 is therefore inhibition of LOC199796 (Accession XM\_058994). Accordingly, utilities of VGAM911 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC199796. Fig. 1 further provides a conceptual descrip-



tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 912 (VGAM912) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34504] VGAM912 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM912 was detected is described hereinabove with reference to Figs. 1–8.

[34505] VGAM912 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Human Herpesvirus 8. VGAM912 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34506] VGAM912 gene encodes a VGAM912 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM912 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM912 precursor RNA is designated SEQ ID:898, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:898 is

located at position 58652 relative to the genome of Human Herpesvirus 8.

[34507] VGAM912 precursor RNA folds onto itself, forming VGAM912 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34508] An enzyme complex designated DICER COMPLEX, `dices` the VGAM912 folded precursor RNA into VGAM912 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM912 RNA is designated SEQ ID:3623, and is provided hereinbelow with reference to the sequence listing part.

[34509] VGAM912 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM912 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM912 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[34510] VGAM912 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM912 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM912 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM912 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM912 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34511] The complementary binding of VGAM912 RNA, herein designated VGAM RNA, to host target binding sites on VGAM912 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM912 host target RNA into VGAM912 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34512] It is appreciated that VGAM912 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM912 host target genes. The mRNA of each one of this plurality of VGAM912 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM912 RNA, herein designated VGAM RNA, and which when bound by VGAM912 RNA causes inhibition of translation of respective one or more VGAM912

host target proteins.

[34513] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM912 gene, herein designated VGAM GENE, on one or more VGAM912 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34514] It is yet further appreciated that a function of VGAM912 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM912 include diagnosis, prevention and treatment of viral infection by Human Herpesvirus 8. Spe-

cific functions, and accordingly utilities, of VGAM912 correlate with, and may be deduced from, the identity of the host target genes which VGAM912 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

- [34515] Nucleotide sequences of the VGAM912 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM912 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM912 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM912 are further described hereinbelow with reference to Table 1.
- [34516] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM912 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM912 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.
- [34517] As mentioned hereinabove with reference to Fig. 1, a function of VGAM912 gene, herein designated VGAM is inhibition of expression of VGAM912 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM912 correlate with, and may be deduced from, the identity of the target genes which VGAM912 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34518] Matrix Metalloproteinase 8 (neutrophil collagenase) (MMP8, Accession NM\_002424) is a VGAM912 host target gene. MMP8 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by MMP8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MMP8 BINDING SITE, designated SEQ ID:8258, to the nucleotide sequence of VGAM912 RNA, herein designated VGAM RNA, also designated SEQ ID:3623.

[34519] A function of VGAM912 is therefore inhibition of Matrix Metalloproteinase 8 (neutrophil collagenase) (MMP8, Accession NM\_002424). Accordingly, utilities of VGAM912 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MMP8. KIAA1024 (Accession XM\_044580) is another VGAM912 host target gene. KIAA1024 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded

by KIAA1024, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1024 BINDING SITE, designated SEQ ID:34235, to the nucleotide sequence of VGAM912 RNA, herein designated VGAM RNA, also designated SEQ ID:3623.

[34520] Another function of VGAM912 is therefore inhibition of KIAA1024 (Accession XM\_044580). Accordingly, utilities of VGAM912 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1024. LOC145820 (Accession XM\_085246) is another VGAM912 host target gene. LOC145820 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC145820, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC145820 BINDING SITE, designated SEQ ID:37992, to the nucleotide sequence of VGAM912 RNA, herein designated VGAM RNA, also designated SEQ ID:3623.

[34521] Another function of VGAM912 is therefore inhibition of LOC145820 (Accession XM\_085246). Accordingly, utilities



of VGAM912 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC145820. LOC151248 (Accession XM\_087143) is another VGAM912 host target gene. LOC151248 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC151248, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151248 BINDING SITE, designated SEQ ID:39087, to the nucleotide sequence of VGAM912 RNA, herein designated VGAM RNA, also designated SEQ ID:3623.

[34522] Another function of VGAM912 is therefore inhibition of LOC151248 (Accession XM\_087143). Accordingly, utilities of VGAM912 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151248. LOC54550 (Accession XM\_085348) is another VGAM912 host target gene. LOC54550 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC54550, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of

LOC54550 BINDING SITE, designated SEQ ID:38076, to the nucleotide sequence of VGAM912 RNA, herein designated VGAM RNA, also designated SEQ ID:3623.

[34523] Another function of VGAM912 is therefore inhibition of LOC54550 (Accession XM\_085348). Accordingly, utilities of VGAM912 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC54550. LOC92539 (Accession XM\_045632) is another VGAM912 host target gene. LOC92539 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92539, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92539 BINDING SITE, designated SEQ ID:34502, to the nucleotide sequence of VGAM912 RNA, herein designated VGAM RNA, also designated SEQ ID:3623.

[34524] Another function of VGAM912 is therefore inhibition of LOC92539 (Accession XM\_045632). Accordingly, utilities of VGAM912 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92539. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the

present invention, referred to here as Viral Genomic Address Messenger 913 (VGAM913) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34525] VGAM913 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM913 was detected is described hereinabove with reference to Figs. 1–8.

[34526] VGAM913 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pothos Latent Virus. VGAM913 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34527] VGAM913 gene encodes a VGAM913 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM913 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM913 precursor RNA is designated SEQ ID:899, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:899 is located at position 2180 relative to the genome of Pothos

Latent Virus.

[34528] VGAM913 precursor RNA folds onto itself, forming VGAM913 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34529] An enzyme complex designated DICER COMPLEX, `dices` the VGAM913 folded precursor RNA into VGAM913 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM913 RNA is designated SEQ ID:3624, and is provided hereinbelow with reference to the sequence listing part.

[34530] VGAM913 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger

RNA, VGAM913 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM913 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34531] VGAM913 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM913 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM913 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM913 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM913 host target RNA, herein designated VGAM HOST TARGET RNA. It is further

appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[34532] The complementary binding of VGAM913 RNA, herein designated VGAM RNA, to host target binding sites on VGAM913 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM913 host target RNA into VGAM913 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34533] It is appreciated that VGAM913 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM913 host target genes. The mRNA of each one of this plurality of VGAM913 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM913 RNA, herein designated VGAM RNA, and which when bound by VGAM913 RNA causes inhibition of translation of respective one or more VGAM913 host target proteins.

[34534] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM913 gene, herein designated VGAM GENE, on one or more VGAM913 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34535] It is yet further appreciated that a function of VGAM913 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM913 include diagnosis, prevention and treatment of viral infection by Pothos Latent Virus. Specific functions, and accordingly utilities, of VGAM913 correlate

with, and may be deduced from, the identity of the host target genes which VGAM913 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34536] Nucleotide sequences of the VGAM913 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM913 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM913 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM913 are further described hereinbelow with reference to Table 1.

[34537] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM913 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM913 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34538] As mentioned hereinabove with reference to Fig. 1, a function of VGAM913 gene, herein designated VGAM is inhibition of expression of VGAM913 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM913 correlate with, and may be deduced



from, the identity of the target genes which VGAM913 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34539] Catenin, Beta Interacting Protein 1 (CTNNBIP1, Accession NM\_020248) is a VGAM913 host target gene. CTNNBIP1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CTNNBIP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CTNNBIP1 BINDING SITE, designated SEQ ID:21547, to the nucleotide sequence of VGAM913 RNA, herein designated VGAM RNA, also designated SEQ ID:3624.

[34540] A function of VGAM913 is therefore inhibition of Catenin, Beta Interacting Protein 1 (CTNNBIP1, Accession NM\_020248). Accordingly, utilities of VGAM913 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CTNNBIP1. Histidyl-tRNA Synthetase 2 (HARS2, Accession NM\_080820) is another VGAM913 host target gene. HARS2 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by HARS2, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HARS2 BINDING SITE, designated SEQ ID:28078, to the nucleotide sequence of VGAM913 RNA, herein designated VGAM RNA, also designated SEQ ID:3624.

[34541] Another function of VGAM913 is therefore inhibition of Histidyl-tRNA Synthetase 2 (HARS2, Accession NM\_080820). Accordingly, utilities of VGAM913 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HARS2. LOC118738 (Accession XM\_061125) is another VGAM913 host target gene. LOC118738 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC118738, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC118738 BINDING SITE, designated SEQ ID:37196, to the nucleotide sequence of VGAM913 RNA, herein designated VGAM RNA, also designated SEQ ID:3624.

[34542] Another function of VGAM913 is therefore inhibition of LOC118738 (Accession XM\_061125). Accordingly, utilities

of VGAM913 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC118738. LOC164684 (Accession XM\_092926) is another VGAM913 host target gene. LOC164684 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC164684, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC164684 BINDING SITE, designated SEQ ID:40159, to the nucleotide sequence of VGAM913 RNA, herein designated VGAM RNA, also designated SEQ ID:3624.

[34543] Another function of VGAM913 is therefore inhibition of LOC164684 (Accession XM\_092926). Accordingly, utilities of VGAM913 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC164684. LOC170425 (Accession XM\_084330) is another VGAM913 host target gene. LOC170425 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC170425, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC170425 BINDING SITE, designated SEQ ID:37552, to the nucleotide sequence of VGAM913 RNA, herein designated VGAM RNA, also designated SEQ ID:3624.

[34544] Another function of VGAM913 is therefore inhibition of LOC170425 (Accession XM\_084330). Accordingly, utilities of VGAM913 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC170425. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 914 (VGAM914) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34545] VGAM914 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM914 was detected is described hereinabove with reference to Figs. 1–8.

[34546] VGAM914 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Pothos Latent Virus. VGAM914 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34547] VGAM914 gene encodes a VGAM914 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM914 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM914 precursor RNA is designated SEQ ID:900, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:900 is located at position 2846 relative to the genome of Pothos Latent Virus.

[34548] VGAM914 precursor RNA folds onto itself, forming VGAM914 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34549] An enzyme complex designated DICER COMPLEX, `dices` the VGAM914 folded precursor RNA into VGAM914 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 60%) nucleotide sequence of VGAM914 RNA is designated SEQ ID:3625, and is provided hereinbelow with reference to the sequence listing part.

[34550] VGAM914 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM914 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM914 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34551] VGAM914 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM914 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM914 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM914 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM914 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[34552] The complementary binding of VGAM914 RNA, herein designated VGAM RNA, to host target binding sites on VGAM914 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM914 host target RNA into VGAM914 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34553] It is appreciated that VGAM914 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM914 host target genes. The mRNA of each one of this plurality of VGAM914 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM914 RNA, herein designated VGAM RNA, and which when bound by VGAM914 RNA causes inhibition of translation of respective one or more VGAM914 host target proteins.

[34554] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM914 gene, herein designated VGAM GENE, on one or more VGAM914 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these



other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[34555] It is yet further appreciated that a function of VGAM914 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of viral infection by Pothos Latent Virus. Specific functions, and accordingly utilities, of VGAM914 correlate with, and may be deduced from, the identity of the host target genes which VGAM914 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34556] Nucleotide sequences of the VGAM914 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM914 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM914 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM914 are further described hereinbelow with reference to Table 1.

[34557] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM914 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM914 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34558] As mentioned hereinabove with reference to Fig. 1, a function of VGAM914 gene, herein designated VGAM is inhibition of expression of VGAM914 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM914 correlate with, and may be deduced from, the identity of the target genes which VGAM914 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34559] Phosphoribosyl Pyrophosphate Synthetase-associated Protein 1 (PRPSAP1, Accession NM\_002766) is a VGAM914 host target gene. PRPSAP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRPSAP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRPSAP1 BINDING SITE, designated SEQ ID:8660, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34560] A function of VGAM914 is therefore inhibition of Phosphoribosyl Pyrophosphate Synthetase-associated Protein 1 (PRPSAP1, Accession NM\_002766), a gene which catalyzes the formation of PRPP from ATP and ribose 5-phosphate. Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRPSAP1. The function of PRPSAP1 has been established by previous studies. Phosphoribosylpyrophosphate (PRPP) synthetase catalyzes the formation of PRPP from ATP and ribose 5-phosphate. Ishizuka et al. (1996) noted that the rat liver enzyme exists as complex aggregates of 34-, 39-, and 41-kD components, with the 34-kD species being the catalytic subunit. The 34-kD subunit from rat liver is a mixture of 2 highly homologous isoforms, PRS I and PRS II. The PRS I and PRS II mRNAs are encoded by 2 distinct genes, designated Prps1 and Prps2. The human PRPS1 (OMIM Ref. No. 311850) and PRPS2 (OMIM Ref. No. 311860) genes are located in different regions of the X chromosome, Xq22-q24 and Xp22.3-p22.2, respectively. The 39- and 41-kD components of these enzymes are termed PRPP synthetase-associated proteins (PAPs). The human 41-kD component, PAP41, is encoded by the PRPSAP2 gene

(OMIM Ref. No. 603762). Since Kita et al. (1994) showed that removal of the Paps from the rat liver enzyme complex led to an increase in enzyme activity of the remaining catalytic subunits, they proposed that Paps have a negative regulatory role in PRPP synthesis. Kita et al. (1994) cloned the cDNA for the 39-kD component (Pap39) from rat liver. The deduced amino acid sequence was remarkably similar to those of the 34-kD subunits. Using a PCR strategy with primers based on the sequence of the rat Pap39 protein, Ishizuka et al. (1996) cloned cDNAs encoding human PAP39. The deduced 356-amino acid human protein shares 98% identity with rat Pap39 and 44% identity with human PRS I and PRS II. Northern blot analysis revealed that PAP39 was expressed as a 2.2-kb mRNA in all human tissues tested. Ishizuka et al. (1996) mapped the human PRPSAP1 gene to 17q24-q25 by PCR analysis of somatic cell hybrids and by fluorescence in situ hybridization.

[34561] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34562] Ishizuka, T.; Ahmad, I.; Kita, K.; Sonoda, T.; Ishijima, S.; Sawa, K.; Suzuki, N.; Tatibana, M. : The human phosphori-

bosylpyrophosphate synthetase-associated protein 39 gene (PRPSAP1) is located in the chromosome region 17q24-q25. Genomics 33: 332-334, 1996. ; and

[34563] Ishizuka, T.; Kita, K.; Sonoda, T.; Ishijima, S.; Sawa, K.; Suzuki, N.; Tatibana, M. : Cloning and sequencing of human complementary DNA for the phosphoribosylpyrophosphate synthetase-as.

[34564] Further studies establishing the function and utilities of PRPSAP1 are found in John Hopkins OMIM database record ID 601249, and in cited publications numbered 9380-9382 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. RAP1B, Member of RAS Oncogene Family (RAP1B, Accession NM\_015646) is another VGAM914 host target gene. RAP1B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RAP1B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAP1B BINDING SITE, designated SEQ ID:17897, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34565] Another function of VGAM914 is therefore inhibition of RAP1B, Member of RAS Oncogene Family (RAP1B, Accession NM\_015646), a gene which induces morphological reversion of a cell line transformed by a ras oncogene. Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAP1B. The function of RAP1B has been established by previous studies. Three human cDNAs encoding 'new' RAS-related proteins, designated RAP1A, RAP1B, and RAP2, were isolated by Pizon et al. (1988). These proteins share approximately 50% amino acid identity with the classical RAS proteins and have numerous structural features in common. The most striking difference between the RAP and RAS proteins resides in their 61st amino acid: glutamine in RAS is replaced by threonine in RAP proteins. Animal model experiments lend further support to the function of RAP1B. Using mice transgenic for constitutive expression of Rap1a within the T cell lineage, Sebzda et al. (2002) found that instead of anergy, these T cells showed enhanced T cell receptor-mediated responses, both in thymocytes and in mature T cells. In addition, Rap1a activation induces strong activation of beta-1 (OMIM Ref. No. 135630) and beta-2 (OMIM

Ref. No. 600065) integrins. The authors concluded that Rap1a positively influences T cells by augmenting their responses and directing integrin activation.

[34566] It is appreciated that the abovementioned animal model for RAP1B is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[34567] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34568] Pizon, V.; Chardin, P.; Lerosey, I.; Olofsson, B.; Tavitian, A. : Human cDNAs RAP1 and RAP2 homologous to the Drosophila gene Dras3 encode proteins closely related to ras in the 'effector' region. Oncogene 3: 201–204, 1988. ; and

[34569] Kitayama, H.; Sugimoto, Y.; Matsuzaki, T.; Ikawa, Y.; Noda, M. : A ras–related gene with transformation suppressor activity. Cell 56: 77–84, 1989. PubMed ID : 2642744 9. Sebzda, E.; Brac.

[34570] Further studies establishing the function and utilities of RAP1B are found in John Hopkins OMIM database record ID 179530, and in cited publications numbered listed in the bibliography section hereinbelow, which are also

hereby incorporated by reference. KIAA0316 (Accession XM\_045712) is another VGAM914 host target gene.

KIAA0316 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0316, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0316 BINDING SITE, designated SEQ ID:34529, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34571] Another function of VGAM914 is therefore inhibition of KIAA0316 (Accession XM\_045712). Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0316. LOC149271 (Accession XM\_086475) is another VGAM914 host target gene. LOC149271 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149271, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149271 BINDING SITE, designated SEQ ID:38681, to



the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34572] Another function of VGAM914 is therefore inhibition of LOC149271 (Accession XM\_086475). Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149271. LOC149372 (Accession XM\_086509) is another VGAM914 host target gene. LOC149372 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC149372, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149372 BINDING SITE, designated SEQ ID:38730, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34573] Another function of VGAM914 is therefore inhibition of LOC149372 (Accession XM\_086509). Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149372. LOC150245 (Accession XM\_097843) is another VGAM914 host target gene. LOC150245 BINDING SITE is HOST TARGET binding site found in the 5' un-

translated region of mRNA encoded by LOC150245, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC150245 BINDING SITE, designated SEQ ID:41160, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34574] Another function of VGAM914 is therefore inhibition of LOC150245 (Accession XM\_097843). Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC150245. LOC153416 (Accession XM\_018473) is another VGAM914 host target gene. LOC153416 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC153416, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153416 BINDING SITE, designated SEQ ID:30362, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34575] Another function of VGAM914 is therefore inhibition of LOC153416 (Accession XM\_018473). Accordingly, utilities

of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153416. LOC196500 (Accession XM\_113734) is another VGAM914 host target gene. LOC196500 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC196500, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC196500 BINDING SITE, designated SEQ ID:42385, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34576] Another function of VGAM914 is therefore inhibition of LOC196500 (Accession XM\_113734). Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC196500. LOC200317 (Accession XM\_114208) is another VGAM914 host target gene. LOC200317 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC200317, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC200317 BINDING SITE, designated SEQ ID:42804, to the nucleotide sequence of VGAM914 RNA, herein designated VGAM RNA, also designated SEQ ID:3625.

[34577] Another function of VGAM914 is therefore inhibition of LOC200317 (Accession XM\_114208). Accordingly, utilities of VGAM914 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200317. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 915 (VGAM915) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34578] VGAM915 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM915 was detected is described hereinabove with reference to Figs. 1–8.

[34579] VGAM915 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Trichoplusia Ni Cytoplasmic Polyhedrosis Virus 15. VGAM915 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34580] VGAM915 gene encodes a VGAM915 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM915 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM915 precursor RNA is designated SEQ ID:901, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:901 is located at position 1864 relative to the genome of Tri-choplusia Ni Cytoplasmic Polyhedrosis Virus 15.

[34581] VGAM915 precursor RNA folds onto itself, forming VGAM915 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34582] An enzyme complex designated DICER COMPLEX, `dices` the VGAM915 folded precursor RNA into VGAM915 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 71%) nucleotide sequence of VGAM915 RNA is designated SEQ ID:3626, and is provided hereinbelow with reference to the sequence listing part.

[34583] VGAM915 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM915 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM915 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34584] VGAM915 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM915 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM915 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM915 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM915 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[34585] The complementary binding of VGAM915 RNA, herein designated VGAM RNA, to host target binding sites on VGAM915 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM915 host target RNA into VGAM915 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34586] It is appreciated that VGAM915 host target gene, herein

designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM915 host target genes. The mRNA of each one of this plurality of VGAM915 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM915 RNA, herein designated VGAM RNA, and which when bound by VGAM915 RNA causes inhibition of translation of respective one or more VGAM915 host target proteins.

[34587] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM915 gene, herein designated VGAM GENE, on one or more VGAM915 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these



other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[34588] It is yet further appreciated that a function of VGAM915 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of viral infection by Trichoplusia Ni Cytoplasmic Polyhedrosis Virus 15. Specific functions, and accordingly utilities, of VGAM915 correlate with, and may be deduced from, the identity of the host target genes which VGAM915 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34589] Nucleotide sequences of the VGAM915 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM915 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM915 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM915 are further described hereinbelow with reference to Table 1.

[34590] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM915 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM915 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34591] As mentioned hereinabove with reference to Fig. 1, a function of VGAM915 gene, herein designated VGAM is inhibition of expression of VGAM915 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM915 correlate with, and may be deduced from, the identity of the target genes which VGAM915 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34592] Caspase Recruitment Domain Family, Member 15 (CARD15, Accession NM\_022162) is a VGAM915 host target gene. CARD15 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CARD15, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CARD15 BINDING SITE, designated SEQ ID:22714, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34593] A function of VGAM915 is therefore inhibition of Caspase Recruitment Domain Family, Member 15 (CARD15, Accession NM\_022162), a gene which serves as an intracellular receptor for bacterial products in monocytes and transduces signals leading to NFkB activation. Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CARD15. The function of CARD15 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM126. CD2-associated Protein (CD2AP, Accession NM\_012120) is another VGAM915 host target gene. CD2AP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CD2AP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CD2AP BINDING SITE, designated SEQ ID:14432, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34594] Another function of VGAM915 is therefore inhibition of CD2-associated Protein (CD2AP, Accession NM\_012120),

a gene which binds CAS ligand and may therefore involve in its growth regulatory pathway. Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CD2AP. The function of CD2AP and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM95. Galactosylceramidase (Krabbe disease) (GALC, Accession NM\_000153) is another VGAM915 host target gene. GALC BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GALC, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GALC BINDING SITE, designated SEQ ID:5663, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34595] Another function of VGAM915 is therefore inhibition of Galactosylceramidase (Krabbe disease) (GALC, Accession NM\_000153), a gene which hydrolyses the galactose ester bonds of galactosylceramide, galactosylsphingosine, lactosylceramide, and monogalactosyldiglyceride. Accordingly, utilities of VGAM915 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with GALC. The function of GALC and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM624. Chromosome 17 Open Reading Frame 31 (C17orf31, Accession NM\_017575) is another VGAM915 host target gene. C17orf31 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by C17orf31, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of C17orf31 BINDING SITE, designated SEQ ID:19008, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34596] Another function of VGAM915 is therefore inhibition of Chromosome 17 Open Reading Frame 31 (C17orf31, Accession NM\_017575). Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C17orf31.

FLJ11362 (Accession NM\_021946) is another VGAM915 host target gene. FLJ11362 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA

encoded by FLJ11362, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ11362 BINDING SITE, designated SEQ ID:22469, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34597] Another function of VGAM915 is therefore inhibition of FLJ11362 (Accession NM\_021946). Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ11362. KIAA0449 (Accession NM\_017596) is another VGAM915 host target gene. KIAA0449 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0449, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0449 BINDING SITE, designated SEQ ID:19055, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34598] Another function of VGAM915 is therefore inhibition of KIAA0449 (Accession NM\_017596). Accordingly, utilities

of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0449. SET Binding Protein 1 (SETBP1, Accession NM\_015559) is another VGAM915 host target gene. SETBP1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SETBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SETBP1 BINDING SITE, designated SEQ ID:17827, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34599] Another function of VGAM915 is therefore inhibition of SET Binding Protein 1 (SETBP1, Accession NM\_015559). Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SETBP1. LOC149302 (Accession XM\_086489) is another VGAM915 host target gene. LOC149302 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC149302, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING

SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149302 BINDING SITE, designated SEQ ID:38703, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34600] Another function of VGAM915 is therefore inhibition of LOC149302 (Accession XM\_086489). Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149302. LOC203378 (Accession XM\_117541) is another VGAM915 host target gene. LOC203378 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC203378, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC203378 BINDING SITE, designated SEQ ID:43546, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34601] Another function of VGAM915 is therefore inhibition of LOC203378 (Accession XM\_117541). Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC203378. LOC256267 (Accession XM\_173007) is another VGAM915 host target gene. LOC256267 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC256267, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256267 BINDING SITE, designated SEQ ID:46277, to the nucleotide sequence of VGAM915 RNA, herein designated VGAM RNA, also designated SEQ ID:3626.

[34602] Another function of VGAM915 is therefore inhibition of LOC256267 (Accession XM\_173007). Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256267. LOC92466 (Accession XM\_045251) is another VGAM915 host target gene. LOC92466 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC92466, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92466 BINDING SITE, designated SEQ ID:34396, to the nucleotide sequence of VGAM915 RNA, herein designated

VGAM RNA, also designated SEQ ID:3626.

[34603] Another function of VGAM915 is therefore inhibition of LOC92466 (Accession XM\_045251). Accordingly, utilities of VGAM915 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC92466. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 916 (VGAM916) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34604] VGAM916 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM916 was detected is described hereinabove with reference to Figs. 1–8.

[34605] VGAM916 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Trichoplusia Ni Cytoplasmic Polyhedrosis Virus 15. VGAM916 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34606] VGAM916 gene encodes a VGAM916 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other

miRNA genes, and unlike most ordinary genes, VGAM916 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM916 precursor RNA is designated SEQ ID:902, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:902 is located at position 762 relative to the genome of Tri-choplusia Ni Cytoplasmic Polyhedrosis Virus 15.

[34607] VGAM916 precursor RNA folds onto itself, forming VGAM916 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34608] An enzyme complex designated DICER COMPLEX, `dices` the VGAM916 folded precursor RNA into VGAM916 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex

comprising an enzyme called Dicer together with other necessary proteins. A probable (over 62%) nucleotide sequence of VGAM916 RNA is designated SEQ ID:3627, and is provided hereinbelow with reference to the sequence listing part.

[34609] VGAM916 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM916 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM916 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34610] VGAM916 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM916 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM916 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and

BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM916 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM916 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34611] The complementary binding of VGAM916 RNA, herein designated VGAM RNA, to host target binding sites on VGAM916 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM916 host target RNA into VGAM916 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34612] It is appreciated that VGAM916 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM916 host target genes. The mRNA of

each one of this plurality of VGAM916 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM916 RNA, herein designated VGAM RNA, and which when bound by VGAM916 RNA causes inhibition of translation of respective one or more VGAM916 host target proteins.

[34613] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM916 gene, herein designated VGAM GENE, on one or more VGAM916 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science

294,779 (2001)).

[34614] It is yet further appreciated that a function of VGAM916 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM916 include diagnosis, prevention and treatment of viral infection by Trichoplusia Ni Cytoplasmic Polyhedrosis Virus 15. Specific functions, and accordingly utilities, of VGAM916 correlate with, and may be deduced from, the identity of the host target genes which VGAM916 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34615] Nucleotide sequences of the VGAM916 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM916 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM916 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM916 are further described hereinbelow with reference to Table 1.

[34616] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM916 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM916 RNA, herein desig-

nated VGAM RNA, are described hereinbelow with reference to Table 2.

[34617] As mentioned hereinabove with reference to Fig. 1, a function of VGAM916 gene, herein designated VGAM is inhibition of expression of VGAM916 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM916 correlate with, and may be deduced from, the identity of the target genes which VGAM916 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34618] Staufen, RNA Binding Protein (Drosophila) (STAU, Accession NM\_004602) is a VGAM916 host target gene. STAU BINDING SITE1 through STAU BINDING SITE4 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by STAU, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAU BINDING SITE1 through STAU BINDING SITE4, designated SEQ ID:10938, SEQ ID:18911, SEQ ID:18917 and SEQ ID:18923 respectively, to the nucleotide sequence of VGAM916 RNA, herein designated VGAM RNA, also designated SEQ ID:3627.



[34619] A function of VGAM916 is therefore inhibition of Staufén, RNA Binding Protein (*Drosophila*) (STAU, Accession NM\_004602), a gene which may play a role in specific positioning of mrnas at given sites in the cell and in stimulating their translation at the site. Accordingly, utilities of VGAM916 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAU. The function of STAU has been established by previous studies. In *Drosophila*, genetic studies have identified a number of potential genes that are necessary for localization of mRNAs in oocytes, one of which is the staufén gene. The staufén gene product is a double-stranded RNA (dsRNA)-binding protein that contains several copies of a consensus dsRNA-binding domain (RBD). By searching an EST database for staufén-related sequences, Wickham et al. (1999) identified a partial cDNA encoding STAU, a human staufén homolog. Using RACE and library screening, they recovered additional cDNAs corresponding to the entire STAU coding region. Northern blot analysis indicated that the STAU gene was expressed as an unresolved band of approximately 3.6 kb in all tissues tested. Characterization of STAU cDNAs revealed that there are 4 different STAU transcripts encoding predicted 496- and 577-amino

acid isoforms differing in their N-terminal extremities. Wickham et al. (1999) also cloned a mouse Stau cDNA. Mouse and human STAU are 90% identical on the amino acid level. The RBDs are well conserved between *Drosophila* and mammalian stau proteins in terms of overall structure and relative positions, and share 47 to 66% identity. However, the mammalian proteins lack the first RBD found in *Drosophila* stau and contain a putative microtubule-binding domain not found in the *Drosophila* protein. In vitro, STAU bound dsRNA and tubulin, suggesting that it crosslinks cytoskeletal and RNA components. In mammalian cells expressing epitope-tagged STAU, immunofluorescence experiments revealed that STAU is localized to the rough endoplasmic reticulum. Wickham et al. (1999) proposed that STAU plays a role in the targeting of RNA to its site of translation. The influenza virus nonstructural protein NS1 is an RNA-binding protein that may be involved in regulatory processes during viral infection, including pre-mRNA splicing, retention of poly(A)-containing RNA in the nucleus, and the stimulation of viral mRNA translation. Using a yeast 2-hybrid screen, Marion et al. (1999) identified stau-like as a protein that bound NS1. By immunofluo-

rescence, they localized endogenous staufen-like to the rough endoplasmic reticulum in HeLa cells. Sedimentation analyses indicated that staufen-like associates with polysomes in these cells. Marion et al. (1999) suggested that staufen-like might therefore play a dual role: positioning specific mRNAs at given sites in the cell, and stimulating their translation at the site.

[34620] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34621] Marion, R. M.; Fortes, P.; Beloso, A.; Dotti, C.; Ortin, J. : A human sequence homologue of staufen is an RNA-binding protein that is associated with polysomes and localizes to the rough endoplasmic reticulum. *Molec. Cell. Biol.* 19: 2212-2219, 1999. ; and

[34622] Wickham, L.; Duchaine, T.; Luo, M.; Nabi, I. R.; DesGroseillers, L. : Mammalian staufen is a double-stranded-RNA- and tubulin-binding protein which localizes to the rough endoplasmic r.

[34623] Further studies establishing the function and utilities of STAU are found in John Hopkins OMIM database record ID 601716, and in cited publications numbered 9115-9117 listed in the bibliography section hereinbelow, which are

also hereby incorporated by reference.FLJ13187 (Accession NM\_024613) is another VGAM916 host target gene. FLJ13187 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ13187, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13187 BINDING SITE, designated SEQ ID:23868, to the nucleotide sequence of VGAM916 RNA, herein designated VGAM RNA, also designated SEQ ID:3627.

[34624] Another function of VGAM916 is therefore inhibition of FLJ13187 (Accession NM\_024613). Accordingly, utilities of VGAM916 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13187. Splicing Factor, Arginine/serine-rich 12 (SFRS12, Accession NM\_139168) is another VGAM916 host target gene. SFRS12 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SFRS12, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRS12 BINDING SITE, designated SEQ

ID:29173, to the nucleotide sequence of VGAM916 RNA, herein designated VGAM RNA, also designated SEQ ID:3627.

[34625] Another function of VGAM916 is therefore inhibition of Splicing Factor, Arginine/serine-rich 12 (SFRS12, Accession NM\_139168). Accordingly, utilities of VGAM916 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRS12. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 917 (VGAM917) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34626] VGAM917 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM917 was detected is described hereinabove with reference to Figs. 1–8.

[34627] VGAM917 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus. VGAM917 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34628] VGAM917 gene encodes a VGAM917 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM917 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM917 precursor RNA is designated SEQ ID:903, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:903 is located at position 134932 relative to the genome of Vaccinia Virus.

[34629] VGAM917 precursor RNA folds onto itself, forming VGAM917 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34630] An enzyme complex designated DICER COMPLEX, `dices` the VGAM917 folded precursor RNA into VGAM917 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a

hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 74%) nucleotide sequence of VGAM917 RNA is designated SEQ ID:3628, and is provided hereinbelow with reference to the sequence listing part.

[34631] VGAM917 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM917 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM917 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34632] VGAM917 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM917 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM917 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an il-

illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM917 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM917 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34633] The complementary binding of VGAM917 RNA, herein designated VGAM RNA, to host target binding sites on VGAM917 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM917 host target RNA into VGAM917 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34634] It is appreciated that VGAM917 host target gene, herein



designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM917 host target genes. The mRNA of each one of this plurality of VGAM917 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM917 RNA, herein designated VGAM RNA, and which when bound by VGAM917 RNA causes inhibition of translation of respective one or more VGAM917 host target proteins.

[34635] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM917 gene, herein designated VGAM GENE, on one or more VGAM917 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these

other miRNA genes have not yet been found (Ruvkun G.,  
`Perspective: Glimpses of a tiny RNA world`, Science  
294,779 (2001)).

[34636] It is yet further appreciated that a function of VGAM917 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM917 correlate with, and may be deduced from, the identity of the host target genes which VGAM917 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34637] Nucleotide sequences of the VGAM917 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM917 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM917 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM917 are further described hereinbelow with reference to Table 1.

[34638] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM917 host target RNA, and schematic

representation of the complementarity of each of these host target binding sites to VGAM917 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34639] As mentioned hereinabove with reference to Fig. 1, a function of VGAM917 gene, herein designated VGAM is inhibition of expression of VGAM917 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM917 correlate with, and may be deduced from, the identity of the target genes which VGAM917 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34640] ATPase, Class V, Type 10B (ATP10B, Accession XM\_032721) is a VGAM917 host target gene. ATP10B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATP10B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATP10B BINDING SITE, designated SEQ ID:31735, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34641] A function of VGAM917 is therefore inhibition of ATPase,

Class V, Type 10B (ATP10B, Accession XM\_032721). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATP10B. BDG-29 (Accession XM\_051343) is another VGAM917 host target gene. BDG-29 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BDG-29, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BDG-29 BINDING SITE, designated SEQ ID:35815, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34642] Another function of VGAM917 is therefore inhibition of BDG-29 (Accession XM\_051343). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BDG-29. GW112 (Accession NM\_006418) is another VGAM917 host target gene. GW112 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GW112, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the

nucleotide sequences of GW112 BINDING SITE, designated SEQ ID:13131, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34643] Another function of VGAM917 is therefore inhibition of GW112 (Accession NM\_006418). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GW112. Heat Shock 27kDa Protein Family, Member 7 (cardiovascular) (HSPB7, Accession NM\_014424) is another VGAM917 host target gene. HSPB7 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HSPB7, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPB7 BINDING SITE, designated SEQ ID:15780, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34644] Another function of VGAM917 is therefore inhibition of Heat Shock 27kDa Protein Family, Member 7 (cardiovascular) (HSPB7, Accession NM\_014424). Accordingly, utilities of VGAM917 include diagnosis, prevention

and treatment of diseases and clinical conditions associated with HSPB7. KIAA1464 (Accession XM\_043069) is another VGAM917 host target gene. KIAA1464 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1464, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1464 BINDING SITE, designated SEQ ID:33882, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34645] Another function of VGAM917 is therefore inhibition of KIAA1464 (Accession XM\_043069). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1464. KIAA1634 (Accession XM\_032749) is another VGAM917 host target gene. KIAA1634 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1634, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1634 BINDING SITE, designated SEQ ID:31752, to the

nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34646] Another function of VGAM917 is therefore inhibition of KIAA1634 (Accession XM\_032749). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1634. Neuropilin (NRP) and Tolloid (TLL)-like 1 (NETO1, Accession NM\_138999) is another VGAM917 host target gene. NETO1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NETO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NETO1 BINDING SITE, designated SEQ ID:29097, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34647] Another function of VGAM917 is therefore inhibition of Neuropilin (NRP) and Tolloid (TLL)-like 1 (NETO1, Accession NM\_138999). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NETO1. PRO2533 (Accession NM\_018629) is another VGAM917 host target

gene. PRO2533 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRO2533, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO2533 BINDING SITE, designated SEQ ID:20703, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.

[34648] Another function of VGAM917 is therefore inhibition of PRO2533 (Accession NM\_018629). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO2533. LOC151201 (Accession XM\_098021) is another VGAM917 host target gene. LOC151201 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC151201, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151201 BINDING SITE, designated SEQ ID:41324, to the nucleotide sequence of VGAM917 RNA, herein designated VGAM RNA, also designated SEQ ID:3628.



[34649] Another function of VGAM917 is therefore inhibition of LOC151201 (Accession XM\_098021). Accordingly, utilities of VGAM917 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151201. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 918 (VGAM918) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34650] VGAM918 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM918 was detected is described hereinabove with reference to Figs. 1–8.

[34651] VGAM918 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM918 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34652] VGAM918 gene encodes a VGAM918 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM918

precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM918 precursor RNA is designated SEQ ID:904, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:904 is located at position 642 relative to the genome of Vaccinia Virus.

[34653] VGAM918 precursor RNA folds onto itself, forming VGAM918 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34654] An enzyme complex designated DICER COMPLEX, `dices` the VGAM918 folded precursor RNA into VGAM918 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other

necessary proteins. A probable (over 76%) nucleotide sequence of VGAM918 RNA is designated SEQ ID:3629, and is provided hereinbelow with reference to the sequence listing part.

[34655] VGAM918 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM918 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM918 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[34656] VGAM918 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM918 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM918 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the

number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM918 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM918 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34657] The complementary binding of VGAM918 RNA, herein designated VGAM RNA, to host target binding sites on VGAM918 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM918 host target RNA into VGAM918 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34658] It is appreciated that VGAM918 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM918 host target genes. The mRNA of each one of this plurality of VGAM918 host target genes

comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM918 RNA, herein designated VGAM RNA, and which when bound by VGAM918 RNA causes inhibition of translation of respective one or more VGAM918 host target proteins.

[34659] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM918 gene, herein designated VGAM GENE, on one or more VGAM918 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34660] It is yet further appreciated that a function of VGAM918 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM918 correlate with, and may be deduced from, the identity of the host target genes which VGAM918 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34661] Nucleotide sequences of the VGAM918 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM918 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM918 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM918 are further described hereinbelow with reference to Table 1.

[34662] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM918 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM918 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34663] As mentioned hereinabove with reference to Fig. 1, a function of VGAM918 gene, herein designated VGAM is inhibition of expression of VGAM918 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM918 correlate with, and may be deduced from, the identity of the target genes which VGAM918 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34664] Myosin IE (MYO1E, Accession NM\_004998) is a VGAM918 host target gene. MYO1E BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MYO1E, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MYO1E BINDING SITE, designated SEQ ID:11441, to the nucleotide sequence of

VGAM918 RNA, herein designated VGAM RNA, also designated SEQ ID:3629.

[34665] A function of VGAM918 is therefore inhibition of Myosin IE (MYO1E, Accession NM\_004998), a gene which is an unconventional myosin. Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MYO1E. The function of MYO1E and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM200. Rho-associated, Coiled-coil Containing Protein Kinase 2 (ROCK2, Accession XM\_038377) is another VGAM918 host target gene. ROCK2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ROCK2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ROCK2 BINDING SITE, designated SEQ ID:32836, to the nucleotide sequence of VGAM918 RNA, herein designated VGAM RNA, also designated SEQ ID:3629.

[34666] Another function of VGAM918 is therefore inhibition of Rho-associated, Coiled-coil Containing Protein Kinase 2



(ROCK2, Accession XM\_038377), a gene which regulates cytokinesis, smooth muscle contraction, the formation of actin stress fibers and focal adhesions. Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ROCK2. The function of ROCK2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM273.MGC15937 (Accession NM\_080661) is another VGAM918 host target gene. MGC15937 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC15937, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15937 BINDING SITE, designated SEQ ID:27949, to the nucleotide sequence of VGAM918 RNA, herein designated VGAM RNA, also designated SEQ ID:3629.

[34667] Another function of VGAM918 is therefore inhibition of MGC15937 (Accession NM\_080661). Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

MGC15937. LOC148029 (Accession XM\_086014) is another VGAM918 host target gene. LOC148029 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC148029, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148029 BINDING SITE, designated SEQ ID:38447, to the nucleotide sequence of VGAM918 RNA, herein designated VGAM RNA, also designated SEQ ID:3629.

[34668] Another function of VGAM918 is therefore inhibition of LOC148029 (Accession XM\_086014). Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148029. LOC169436 (Accession XM\_095696) is another VGAM918 host target gene. LOC169436 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC169436, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC169436 BINDING SITE, designated SEQ ID:40279, to the nucleotide sequence of VGAM918 RNA, herein desig-

nated VGAM RNA, also designated SEQ ID:3629.

[34669] Another function of VGAM918 is therefore inhibition of LOC169436 (Accession XM\_095696). Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC169436. LOC256267 (Accession XM\_173007) is another VGAM918 host target gene. LOC256267 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC256267, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256267 BINDING SITE, designated SEQ ID:46276, to the nucleotide sequence of VGAM918 RNA, herein designated VGAM RNA, also designated SEQ ID:3629.

[34670] Another function of VGAM918 is therefore inhibition of LOC256267 (Accession XM\_173007). Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256267. LOC257426 (Accession XM\_039451) is another VGAM918 host target gene. LOC257426 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC257426, cor-

responding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC257426 BINDING SITE, designated SEQ ID:33098, to the nucleotide sequence of VGAM918 RNA, herein designated VGAM RNA, also designated SEQ ID:3629.

[34671] Another function of VGAM918 is therefore inhibition of LOC257426 (Accession XM\_039451). Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC257426. LOC92466 (Accession XM\_045251) is another VGAM918 host target gene. LOC92466 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC92466, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC92466 BINDING SITE, designated SEQ ID:34395, to the nucleotide sequence of VGAM918 RNA, herein designated VGAM RNA, also designated SEQ ID:3629.

[34672] Another function of VGAM918 is therefore inhibition of LOC92466 (Accession XM\_045251). Accordingly, utilities of VGAM918 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with LOC92466. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 919 (VGAM919) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34673] VGAM919 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM919 was detected is described hereinabove with reference to Figs. 1–8.

[34674] VGAM919 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM919 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34675] VGAM919 gene encodes a VGAM919 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM919 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM919 precursor RNA is designated SEQ

ID:905, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:905 is located at position 963 relative to the genome of Vaccinia Virus.

[34676] VGAM919 precursor RNA folds onto itself, forming VGAM919 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34677] An enzyme complex designated DICER COMPLEX, `dices` the VGAM919 folded precursor RNA into VGAM919 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM919 RNA is designated SEQ ID:3630, and is provided hereinbelow with reference to the sequence

listing part.

[34678] VGAM919 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM919 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM919 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34679] VGAM919 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM919 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM919 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM919 RNA, herein designated VGAM RNA, may

have a different number of host target binding sites in untranslated regions of a VGAM919 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34680] The complementary binding of VGAM919 RNA, herein designated VGAM RNA, to host target binding sites on VGAM919 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM919 host target RNA into VGAM919 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34681] It is appreciated that VGAM919 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM919 host target genes. The mRNA of each one of this plurality of VGAM919 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM919 RNA, herein designated VGAM



RNA, and which when bound by VGAM919 RNA causes inhibition of translation of respective one or more VGAM919 host target proteins.

[34682] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM919 gene, herein designated VGAM GENE, on one or more VGAM919 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34683] It is yet further appreciated that a function of VGAM919 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly,

utilities of VGAM919 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM919 correlate with, and may be deduced from, the identity of the host target genes which VGAM919 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34684] Nucleotide sequences of the VGAM919 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM919 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM919 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM919 are further described hereinbelow with reference to Table 1.

[34685] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM919 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM919 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34686] As mentioned hereinabove with reference to Fig. 1, a function of VGAM919 gene, herein designated VGAM is

inhibition of expression of VGAM919 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM919 correlate with, and may be deduced from, the identity of the target genes which VGAM919 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34687] LOC152078 (Accession XM\_087376) is a VGAM919 host target gene. LOC152078 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152078 BINDING SITE, designated SEQ ID:39213, to the nucleotide sequence of VGAM919 RNA, herein designated VGAM RNA, also designated SEQ ID:3630.

[34688] A function of VGAM919 is therefore inhibition of LOC152078 (Accession XM\_087376). Accordingly, utilities of VGAM919 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152078. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Ad-

dress Messenger 920 (VGAM920) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34689] VGAM920 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM920 was detected is described hereinabove with reference to Figs. 1–8.

[34690] VGAM920 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Vaccinia Virus.

VGAM920 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34691] VGAM920 gene encodes a VGAM920 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM920 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM920 precursor RNA is designated SEQ ID:906, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:906 is located at position 1243 relative to the genome of Vaccinia Virus.

[34692] VGAM920 precursor RNA folds onto itself, forming VGAM920 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34693] An enzyme complex designated DICER COMPLEX, `dices` the VGAM920 folded precursor RNA into VGAM920 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 41%) nucleotide sequence of VGAM920 RNA is designated SEQ ID:3631, and is provided hereinbelow with reference to the sequence listing part.

[34694] VGAM920 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM920 host target RNA, herein designated VGAM

HOST TARGET RNA. VGAM920 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34695] VGAM920 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM920 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM920 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM920 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM920 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding

sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34696] The complementary binding of VGAM920 RNA, herein designated VGAM RNA, to host target binding sites on VGAM920 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM920 host target RNA into VGAM920 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34697] It is appreciated that VGAM920 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM920 host target genes. The mRNA of each one of this plurality of VGAM920 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM920 RNA, herein designated VGAM RNA, and which when bound by VGAM920 RNA causes inhibition of translation of respective one or more VGAM920 host target proteins.

[34698] It is further appreciated by one skilled in the art that the

mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM920 gene, herein designated VGAM GENE, on one or more VGAM920 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34699] It is yet further appreciated that a function of VGAM920 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM920 include diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM920 correlate with, and may be deduced from, the identity of the host



target genes which VGAM920 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34700] Nucleotide sequences of the VGAM920 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM920 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM920 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM920 are further described hereinbelow with reference to Table 1.

[34701] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM920 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM920 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34702] As mentioned hereinabove with reference to Fig. 1, a function of VGAM920 gene, herein designated VGAM is inhibition of expression of VGAM920 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM920 correlate with, and may be deduced from, the identity of the target genes which VGAM920

binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34703] LOC152078 (Accession XM\_087376) is a VGAM920 host target gene. LOC152078 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152078, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152078 BINDING SITE, designated SEQ ID:39213, to the nucleotide sequence of VGAM920 RNA, herein designated VGAM RNA, also designated SEQ ID:3631.

[34704] A function of VGAM920 is therefore inhibition of LOC152078 (Accession XM\_087376). Accordingly, utilities of VGAM920 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152078. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 921 (VGAM921) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34705] VGAM921 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM921 was detected is described hereinabove with reference to Figs. 1–8.

[34706] VGAM921 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Peanut Clump Virus. VGAM921 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34707] VGAM921 gene encodes a VGAM921 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM921 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM921 precursor RNA is designated SEQ ID:907, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:907 is located at position 3787 relative to the genome of Peanut Clump Virus.

[34708] VGAM921 precursor RNA folds onto itself, forming VGAM921 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this

‘hairpin structure’, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed–reversed sequence of the nucleotide sequence of the second half thereof.

[34709] An enzyme complex designated DICER COMPLEX, ‘dices’ the VGAM921 folded precursor RNA into VGAM921 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, ‘dicing’ of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 44%) nucleotide sequence of VGAM921 RNA is designated SEQ ID:3632, and is provided hereinbelow with reference to the sequence listing part.

[34710] VGAM921 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM921 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM921 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5’ untranslated region, a protein coding region and a 3’ untranslated region, designated 5’UTR, PROTEIN

CODING and 3`UTR respectively.

[34711] VGAM921 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM921 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM921 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM921 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM921 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34712] The complementary binding of VGAM921 RNA, herein designated VGAM RNA, to host target binding sites on VGAM921 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM921 host target RNA into VGAM921 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34713] It is appreciated that VGAM921 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM921 host target genes. The mRNA of each one of this plurality of VGAM921 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM921 RNA, herein designated VGAM RNA, and which when bound by VGAM921 RNA causes inhibition of translation of respective one or more VGAM921 host target proteins.

[34714] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM921 gene, herein designated VGAM GENE, on one or more VGAM921 host target gene, herein designated

VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34715] It is yet further appreciated that a function of VGAM921 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of viral infection by Peanut Clump Virus. Specific functions, and accordingly utilities, of VGAM921 correlate with, and may be deduced from, the identity of the host target genes which VGAM921 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34716] Nucleotide sequences of the VGAM921 precursor RNA,

herein designated VGAM PRECURSOR RNA, and of the  
`diced` VGAM921 RNA, herein designated VGAM RNA,  
and a schematic representation of the secondary folding  
of VGAM921 folded precursor RNA, herein designated  
VGAM FOLDED PRECURSOR RNA, of VGAM921 are further  
described hereinbelow with reference to Table 1.

[34717] Nucleotide sequences of host target binding sites, such as  
BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of  
Fig. 1, found on VGAM921 host target RNA, and schematic  
representation of the complementarity of each of these  
host target binding sites to VGAM921 RNA, herein desig-  
nated VGAM RNA, are described hereinbelow with refer-  
ence to Table 2.

[34718] As mentioned hereinabove with reference to Fig. 1, a  
function of VGAM921 gene, herein designated VGAM is  
inhibition of expression of VGAM921 target genes. It is  
appreciated that specific functions, and accordingly utili-  
ties, of VGAM921 correlate with, and may be deduced  
from, the identity of the target genes which VGAM921  
binds and inhibits, and the function of these target genes,  
as elaborated hereinbelow.

[34719] Adenylosuccinate Synthase (ADSS, Accession XM\_049992)  
is a VGAM921 host target gene. ADSS BINDING SITE is



HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADSS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADSS BINDING SITE, designated SEQ ID:35541, to the nucleotide sequence of VGAM921 RNA, herein designated VGAM RNA, also designated SEQ ID:3632.

[34720] A function of VGAM921 is therefore inhibition of Adenylosuccinate Synthase (ADSS, Accession XM\_049992), a gene which plays an important role in the de novo pathway of purine nucleotide biosynthesis. Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADSS. The function of ADSS has been established by previous studies. Somatic cell hybrids between human cells and Chinese hamster ovary cells deficient in specific steps in the purine biosynthetic pathway permitted mapping of human genes correcting the defects. The ade(-)H mutant is missing the enzyme adenylosuccinate synthetase (IMP:L-aspartate ligase; EC 6.3.4.4.), which carries out the first of a 2-step sequence in the biosynthesis of AMP from IMP. Thus, ade(-)H cells require exogenous adenine for growth. Lai et

al. (1989) found that in somatic cell hybrids human chromosome 1 corrected the defect so that the hybrid cell containing chromosome 1 grew without adenine. Lai et al. (1991) reported that analysis of a human/CHO translocation chromosome that arose in 1 of the hybrids suggested that the gene correcting the defect lies in the region 1cen-q12. (See their Figure 1 for a useful diagram of the purine biosynthesis pathway and the purine nucleotide cycle pathway, together with the location of the genes for the enzymes when known.) AMP deaminase, which converts AMP back to IMP, is coded by a gene, perhaps 2 genes, in region 1p21-p13; see 102770. From a human liver library, Powell et al. (1992) isolated a cDNA that encoded a protein of 455 amino acids. Alignment with the sequence of the ADSS gene in mouse, *Dictyostelium discoideum*, and *E. coli* pointed to invariant residues that are likely to be important for structure and/or catalysis. The human ADSS sequence also showed some similarity to argininosuccinate synthetase, which catalyzes a chemically similar reaction.

[34721] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

- [34722] Lai, L.-W.; Hart, I. M.; Patterson, D. : A gene correcting the defect in the CHO mutant Ade(-)H, deficient in a branch point enzyme (adenylosuccinate synthetase) of de novo purine biosynthesis, is located on the long arm of chromosome 1. *Genomics* 9: 322-328, 1991. ; and
- [34723] Powell, S. M.; Zalkin, H.; Dixon, J. E. : Cloning and characterization of the cDNA encoding human adenylosuccinate synthetase. *FEBS Lett.* 303: 4-10, 1992.
- [34724] Further studies establishing the function and utilities of ADSS are found in John Hopkins OMIM database record ID 103060, and in cited publications numbered 489-491 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. LIM Domain Only 7 (LMO7, Accession NM\_015843) is another VGAM921 host target gene. LMO7 BINDING SITE1 and LMO7 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by LMO7, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LMO7 BINDING SITE1 and LMO7 BINDING SITE2, designated SEQ ID:17971 and SEQ ID:11828 respectively, to the nucleotide sequence of VGAM921 RNA, herein designated

VGAM RNA, also designated SEQ ID:3632.

[34725] Another function of VGAM921 is therefore inhibition of LIM Domain Only 7 (LMO7, Accession NM\_015843). Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LMO7. RNA Guanylyltransferase and 5'-phosphatase (RNGTT, Accession NM\_003800) is another VGAM921 host target gene. RNGTT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNGTT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNGTT BINDING SITE, designated SEQ ID:9895, to the nucleotide sequence of VGAM921 RNA, herein designated VGAM RNA, also designated SEQ ID:3632.

[34726] Another function of VGAM921 is therefore inhibition of RNA Guanylyltransferase and 5'-phosphatase (RNGTT, Accession NM\_003800), a gene which is an mRNA capping enzyme; bifunctional enzyme containing both 5'-triphosphatase and mRNA guanylyltransferase activity. Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of diseases and clinical conditions

associated with RNGTT. The function of RNGTT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM292.FLJ14906 (Accession NM\_032859) is another VGAM921 host target gene.

FLJ14906 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ14906, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ14906 BINDING SITE, designated SEQ ID:26662, to the nucleotide sequence of VGAM921 RNA, herein designated VGAM RNA, also designated SEQ ID:3632.

[34727] Another function of VGAM921 is therefore inhibition of FLJ14906 (Accession NM\_032859). Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14906. KIAA1727 (Accession XM\_034262) is another VGAM921 host target gene. KIAA1727 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by KIAA1727, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1727 BINDING SITE, designated SEQ ID:32036, to the nucleotide sequence of VGAM921 RNA, herein designated VGAM RNA, also designated SEQ ID:3632.

[34728] Another function of VGAM921 is therefore inhibition of KIAA1727 (Accession XM\_034262). Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1727. KIAA1854 (Accession XM\_049884) is another VGAM921 host target gene. KIAA1854 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1854, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1854 BINDING SITE, designated SEQ ID:35524, to the nucleotide sequence of VGAM921 RNA, herein designated VGAM RNA, also designated SEQ ID:3632.

[34729] Another function of VGAM921 is therefore inhibition of KIAA1854 (Accession XM\_049884). Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1854. LOC153114 (Accession XM\_098313) is another VGAM921 host target gene. LOC153114 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC153114, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC153114 BINDING SITE, designated SEQ ID:41573, to the nucleotide sequence of VGAM921 RNA, herein designated VGAM RNA, also designated SEQ ID:3632.

[34730] Another function of VGAM921 is therefore inhibition of LOC153114 (Accession XM\_098313). Accordingly, utilities of VGAM921 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC153114. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 922 (VGAM922) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34731] VGAM922 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM922 was detected is described hereinabove with reference to Figs. 1–8.

[34732] VGAM922 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Peanut Clump Virus.

VGAM922 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34733] VGAM922 gene encodes a VGAM922 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM922 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM922 precursor RNA is designated SEQ ID:908, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:908 is located at position 1130 relative to the genome of Peanut Clump Virus.

[34734] VGAM922 precursor RNA folds onto itself, forming VGAM922 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence



of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34735] An enzyme complex designated DICER COMPLEX, `dices` the VGAM922 folded precursor RNA into VGAM922 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 45%) nucleotide sequence of VGAM922 RNA is designated SEQ ID:3633, and is provided hereinbelow with reference to the sequence listing part.

[34736] VGAM922 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM922 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM922 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34737] VGAM922 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM922 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM922 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM922 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM922 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[34738] The complementary binding of VGAM922 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM922 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM922 host target RNA into VGAM922 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34739] It is appreciated that VGAM922 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM922 host target genes. The mRNA of each one of this plurality of VGAM922 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM922 RNA, herein designated VGAM RNA, and which when bound by VGAM922 RNA causes inhibition of translation of respective one or more VGAM922 host target proteins.

[34740] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM922 gene, herein designated VGAM GENE, on one or more VGAM922 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34741] It is yet further appreciated that a function of VGAM922 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of viral infection by Peanut Clump Virus. Specific functions, and accordingly utilities, of VGAM922 correlate with, and may be deduced from, the identity of the host target genes which VGAM922 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34742] Nucleotide sequences of the VGAM922 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM922 RNA, herein designated VGAM RNA,

and a schematic representation of the secondary folding of VGAM922 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM922 are further described hereinbelow with reference to Table 1.

[34743] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM922 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM922 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34744] As mentioned hereinabove with reference to Fig. 1, a function of VGAM922 gene, herein designated VGAM is inhibition of expression of VGAM922 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM922 correlate with, and may be deduced from, the identity of the target genes which VGAM922 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34745] Notch Homolog 2 (Drosophila) (NOTCH2, Accession NM\_024408) is a VGAM922 host target gene. NOTCH2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NOTCH2,

corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NOTCH2 BINDING SITE, designated SEQ ID:23651, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34746] A function of VGAM922 is therefore inhibition of Notch Homolog 2 (Drosophila) (NOTCH2, Accession NM\_024408), a gene which is moderately similar to a region of murine Notch1 and contains an ankyrin repeat. Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NOTCH2. The function of NOTCH2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM93. Polymerase (DNA directed), Theta (POLQ, Accession NM\_006596) is another VGAM922 host target gene. POLQ BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by POLQ, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of POLQ BINDING SITE, designated SEQ ID:13368, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34747] Another function of VGAM922 is therefore inhibition of Polymerase (DNA directed), Theta (POLQ, Accession NM\_006596), a gene which enhances untargeted mutagenesis. Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with POLQ. The function of POLQ has been established by previous studies. By EST database searching for homologs of yeast Rad30 and screening of a fetal brain cDNA library, Johnson et al. (2000) also cloned POLK, which they termed POL-theta (POLQ) because it encodes the eighth known eukaryotic polymerase. Functional analysis showed that purified POLK can incorporate all 4 nucleotides almost to the end of the template. In contrast to POLH, POLK, which lacks a proofreading exonuclease function, is unable to bypass DNA lesions, namely cis-syn T-T dimers, T-T photoproducts, or an abasic site. Assays of fidelity of replication indicated that POLK misincorporated deoxynucleotides with a frequency of 1/1000 to 1/10,000, a rate 10-fold lower than that of POLH. Ohashi

et al. (2000) also found that POLK is unable to bypass T-T dimers. Unlike Johnson et al. (2000), however, they did observe bypassing of abasic sites, the most common lesions in DNA within cells which are generated by spontaneous hydrolysis of the N glycoside bond during the course of repairing base-damage generated by carcinogenic agents and ionizing radiation. Ohashi et al. (2000) noted that their finding was heavily dependent on sequence context and enzyme concentration.

[34748] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34749] Johnson, R. E.; Prakash, S.; Prakash, L. : The human DINB1 gene encodes the DNA polymerase Pol-theta. Proc. Nat. Acad. Sci. 97: 3838-3843, 2000. ; and

[34750] Ohashi, E.; Ogi, T.; Kusumoto, R.; Iwai, S.; Masutani, C.; Hanaoka, F.; Ohmori, H. : Error-prone bypass of certain DNA lesions by the human DNA polymerase kappa. Genes Dev. 14: 1589-1594.

[34751] Further studies establishing the function and utilities of POLQ are found in John Hopkins OMIM database record ID 605650, and in cited publications numbered 411-414 listed in the bibliography section hereinbelow, which are



also hereby incorporated by reference. RAD1 Homolog (*S. pombe*) (RAD1, Accession NM\_133282) is another VGAM922 host target gene. RAD1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by RAD1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RAD1 BINDING SITE, designated SEQ ID:28436, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34752] Another function of VGAM922 is therefore inhibition of RAD1 Homolog (*S. pombe*) (RAD1, Accession NM\_133282), a gene which has important roles in DNA damage-activated mitotic and meiotic cell cycle checkpoints. Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RAD1. The function of RAD1 has been established by previous studies. In the fission yeast *S. pombe*, the *rad1+* gene product is required for DNA repair and replication. Parker et al. (1998) cloned 2 alternatively spliced human cDNAs encoding proteins with significant homology to yeast *rad1+*. The longer cDNA, called

Hrad1A, encodes a 282–amino acid polypeptide, while Hrad1B encodes a 163–amino acid polypeptide. Northern blot analysis revealed that human RAD1 is expressed as mRNAs of 5, 3, and 1.3 kb in a variety of human tissues, with higher levels present in some cancer cell lines.

Northern blot analysis of cells subjected to ultraviolet radiation demonstrated that human RAD1 expression is not induced in response to DNA damage. Purified RAD1 exhibited terminal exonuclease activity on double–stranded DNA, with a preference for 3–prime ends. Independently, Udell et al. (1998) isolated RAD1 cDNAs from a spontaneously transformed human keratinocyte cDNA library. The cDNAs encode the 282–amino acid RAD1 isoform, which is 90% and 27% identical to mouse Rad1 and *S. pombe rad1+*, respectively. Udell et al. (1998) found that expression of human RAD1 in yeast *rad1* mutants partially restores radiation resistance and G2 checkpoint proficiency.

[34753] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34754] Parker, A. E.; Van de Weyer, I.; Laus, M. C.; Oostveen, I.; Yon, J.; Verhasselt, P.; Luyten, W. H. M. L. : A human ho–

mologue of *Schizosaccharomyces pombe* rad1+ checkpoint gene encodes an exonuclease. J. Biol. Chem. 273: 18332–18339, 1998. ; and

[34755] Udell, C. M.; Lee, S. K.; Davey, S. : HRAD1 and MRAD1 encode mammalian homologues of the fission yeast rad1+ cell cycle checkpoint control gene. Nucleic Acids Res. 26: 3971–3976, 1998.

[34756] Further studies establishing the function and utilities of RAD1 are found in John Hopkins OMIM database record ID 603153, and in cited publications numbered 690, 543 and 2422 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.

RNA (guanine-7-) Methyltransferase (RNMT, Accession NM\_003799) is another VGAM922 host target gene. RNMT BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by RNMT, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RNMT BINDING SITE, designated SEQ ID:9890, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34757] Another function of VGAM922 is therefore inhibition of

RNA (guanine-7-) Methyltransferase (RNMT, Accession NM\_003799), a gene which catalyzes the methylation of GpppN- at the guanine N7 position. Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RNMT. The function of RNMT and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178.SIP (Accession NM\_014412) is another VGAM922 host target gene. SIP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SIP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SIP BINDING SITE, designated SEQ ID:15759, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34758] Another function of VGAM922 is therefore inhibition of SIP (Accession NM\_014412). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SIP. Solute Carrier Family 38, Member 3 (SLC38A3, Accession

NM\_006841) is another VGAM922 host target gene. SLC38A3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC38A3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC38A3 BINDING SITE, designated SEQ ID:13714, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34759] Another function of VGAM922 is therefore inhibition of Solute Carrier Family 38, Member 3 (SLC38A3, Accession NM\_006841), a gene which involves H<sup>+</sup> exchange and Na<sup>+</sup> cotransport, mediates glutamine efflux and uptake. Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC38A3. The function of SLC38A3 has been established by previous studies. The amino acid glutamine has a central role in nitrogen metabolism. Although the molecular mechanisms responsible for its transport across cell membranes are poorly understood, classical amino acid transport system N appears particularly important. Using intracellular pH measurements,

Chaudhry et al. (1999) identified an orphan protein, which they called SN1, related to the vesicular GABA transporter (VGAT) as system N. Functional analysis by Chaudhry et al. (1999) showed that this protein involves H<sup>+</sup> exchange as well as Na<sup>+</sup> cotransport and, under physiologic conditions, mediates glutamine efflux as well as uptake. Together with the pattern of SN1 expression, these unusual properties suggested novel physiologic roles for system N in nitrogen metabolism and synaptic transmission

[34760] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34761] Chaudhry, F. A.; Reimer, R. J.; Krizaj, D.; Barber, D.; Storm-Mathisen, J.; Copenhagen, D. R.; Edwards, R. H. : Molecular analysis of system N suggests novel physiological roles in nitrogen metabolism and synaptic transmission. Cell 99: 769–780, 1999. ; and

[34762] Lerman, M. I.; Minna, J. D. : The 630-kb lung cancer homozygous deletion region on human chromosome 3p21.3: identification and evaluation of the resident candidate tumor suppressor genes.

[34763] Further studies establishing the function and utilities of SLC38A3 are found in John Hopkins OMIM database

record ID 604437, and in cited publications numbered 7939 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cdc42 Guanine Nucleotide Exchange Factor (GEF) 9 (ARHGEF9, Accession NM\_015185) is another VGAM922 host target gene.

ARHGEF9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGEF9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGEF9 BINDING SITE, designated SEQ ID:17544, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34764] Another function of VGAM922 is therefore inhibition of Cdc42 Guanine Nucleotide Exchange Factor (GEF) 9 (ARHGEF9, Accession NM\_015185). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGEF9. CG018 (Accession NM\_052818) is another VGAM922 host target gene. CG018 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CG018, corresponding to a HOST

TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CG018 BINDING SITE, designated SEQ ID:27401, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34765] Another function of VGAM922 is therefore inhibition of CG018 (Accession NM\_052818). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CG018. DKFZP434J214 (Accession XM\_027639) is another VGAM922 host target gene. DKFZP434J214 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by DKFZP434J214, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP434J214 BINDING SITE, designated SEQ ID:30550, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34766] Another function of VGAM922 is therefore inhibition of DKFZP434J214 (Accession XM\_027639). Accordingly, utilities of VGAM922 include diagnosis, prevention and treat-



ment of diseases and clinical conditions associated with DKFZP434J214. HCA127 (Accession NM\_018684) is another VGAM922 host target gene. HCA127 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HCA127, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCA127 BINDING SITE, designated SEQ ID:20760, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34767] Another function of VGAM922 is therefore inhibition of HCA127 (Accession NM\_018684). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCA127. KIAA0931 (Accession XM\_041191) is another VGAM922 host target gene. KIAA0931 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0931, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0931 BINDING SITE, designated SEQ ID:33488, to the nucleotide sequence of

VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34768] Another function of VGAM922 is therefore inhibition of KIAA0931 (Accession XM\_041191). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0931. KIAA1795 (Accession XM\_050988) is another VGAM922 host target gene. KIAA1795 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1795, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1795 BINDING SITE, designated SEQ ID:35702, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34769] Another function of VGAM922 is therefore inhibition of KIAA1795 (Accession XM\_050988). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1795. MGC5457 (Accession NM\_032633) is another VGAM922 host target gene. MGC5457 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by MGC5457, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC5457 BINDING SITE, designated SEQ ID:26348, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34770] Another function of VGAM922 is therefore inhibition of MGC5457 (Accession NM\_032633). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC5457. NYD-SP27 (Accession NM\_033123) is another VGAM922 host target gene. NYD-SP27 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by NYD-SP27, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NYD-SP27 BINDING SITE, designated SEQ ID:26969, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34771] Another function of VGAM922 is therefore inhibition of NYD-SP27 (Accession NM\_033123). Accordingly, utilities

of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NYD-SP27. PRO0132 (Accession NM\_014116) is another VGAM922 host target gene. PRO0132 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PRO0132, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRO0132 BINDING SITE, designated SEQ ID:15369, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34772] Another function of VGAM922 is therefore inhibition of PRO0132 (Accession NM\_014116). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRO0132. SHAPY (Accession NM\_138793) is another VGAM922 host target gene. SHAPY BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by SHAPY, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SHAPY BINDING SITE, designated SEQ

ID:29016, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34773] Another function of VGAM922 is therefore inhibition of SHAPY (Accession NM\_138793). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SHAPY. UCK1 (Accession NM\_031432) is another VGAM922 host target gene. UCK1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by UCK1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UCK1 BINDING SITE, designated SEQ ID:25428, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34774] Another function of VGAM922 is therefore inhibition of UCK1 (Accession NM\_031432). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UCK1. WD Repeat Domain 9 (WDR9, Accession NM\_018963) is another VGAM922 host target gene. WDR9 BINDING SITE is

HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by WDR9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of WDR9 BINDING SITE, designated SEQ ID:21034, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34775] Another function of VGAM922 is therefore inhibition of WD Repeat Domain 9 (WDR9, Accession NM\_018963). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with WDR9. LOC143465 (Accession XM\_096430) is another VGAM922 host target gene. LOC143465 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC143465, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC143465 BINDING SITE, designated SEQ ID:40367, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34776] Another function of VGAM922 is therefore inhibition of

LOC143465 (Accession XM\_096430). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC143465. LOC159963 (Accession XM\_089960) is another VGAM922 host target gene. LOC159963 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC159963, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC159963 BINDING SITE, designated SEQ ID:39988, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34777] Another function of VGAM922 is therefore inhibition of LOC159963 (Accession XM\_089960). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC159963. LOC200609 (Accession XM\_117256) is another VGAM922 host target gene. LOC200609 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC200609, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC200609 BINDING SITE, designated SEQ ID:43340, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34778] Another function of VGAM922 is therefore inhibition of LOC200609 (Accession XM\_117256). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200609. LOC222237 (Accession XM\_168592) is another VGAM922 host target gene. LOC222237 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC222237, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222237 BINDING SITE, designated SEQ ID:45270, to the nucleotide sequence of VGAM922 RNA, herein designated VGAM RNA, also designated SEQ ID:3633.

[34779] Another function of VGAM922 is therefore inhibition of LOC222237 (Accession XM\_168592). Accordingly, utilities of VGAM922 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC222237. Fig. 1 further provides a conceptual descrip-



tion of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 923 (VGAM923) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34780] VGAM923 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM923 was detected is described hereinabove with reference to Figs. 1–8.

[34781] VGAM923 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Peanut Clump Virus. VGAM923 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34782] VGAM923 gene encodes a VGAM923 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM923 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM923 precursor RNA is designated SEQ ID:909, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:909 is

located at position 1684 relative to the genome of Peanut Clump Virus.

[34783] VGAM923 precursor RNA folds onto itself, forming VGAM923 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34784] An enzyme complex designated DICER COMPLEX, `dices` the VGAM923 folded precursor RNA into VGAM923 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 77%) nucleotide sequence of VGAM923 RNA is designated SEQ ID:3634, and is provided hereinbelow with reference to the sequence listing part.

[34785] VGAM923 host target gene, herein designated VGAM

HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM923 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM923 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5' UTR, PROTEIN CODING and 3' UTR respectively.

[34786] VGAM923 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM923 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM923 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM923 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM923 host target RNA,

herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34787] The complementary binding of VGAM923 RNA, herein designated VGAM RNA, to host target binding sites on VGAM923 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM923 host target RNA into VGAM923 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34788] It is appreciated that VGAM923 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM923 host target genes. The mRNA of each one of this plurality of VGAM923 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM923 RNA, herein designated VGAM RNA, and which when bound by VGAM923 RNA causes inhibition of translation of respective one or more VGAM923

host target proteins.

[34789] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM923 gene, herein designated VGAM GENE, on one or more VGAM923 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34790] It is yet further appreciated that a function of VGAM923 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of viral infection by Peanut Clump Virus. Spe-

cific functions, and accordingly utilities, of VGAM923 correlate with, and may be deduced from, the identity of the host target genes which VGAM923 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34791] Nucleotide sequences of the VGAM923 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM923 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM923 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM923 are further described hereinbelow with reference to Table 1.

[34792] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM923 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM923 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34793] As mentioned hereinabove with reference to Fig. 1, a function of VGAM923 gene, herein designated VGAM is inhibition of expression of VGAM923 target genes. It is appreciated that specific functions, and accordingly utili-

ties, of VGAM923 correlate with, and may be deduced from, the identity of the target genes which VGAM923 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34794] A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 4 (ADAMTS4, Accession NM\_005099) is a VGAM923 host target gene. ADAMTS4 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADAMTS4, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADAMTS4 BINDING SITE, designated SEQ ID:11565, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34795] A function of VGAM923 is therefore inhibition of A Disintegrin-like and Metalloprotease (reprolysin type) with Thrombospondin Type 1 Motif, 4 (ADAMTS4, Accession NM\_005099), a gene which cleaves aggrecan, a cartilage proteoglycan, and may be involved in its turnover. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions as-

sociated with ADAMTS4. The function of ADAMTS4 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM809. Adenylate Cyclase 6 (ADCY6, Accession NM\_015270) is another VGAM923 host target gene. ADCY6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ADCY6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADCY6 BINDING SITE, designated SEQ ID:17584, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34796] Another function of VGAM923 is therefore inhibition of Adenylate Cyclase 6 (ADCY6, Accession NM\_015270), a gene which is a membrane-bound,  $Ca^{2+}$ -inhibitable adenylyl cyclase (by similarity). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADCY6. The function of ADCY6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference



to VGAM22. Apoptotic Protease Activating Factor (APAF1, Accession NM\_013229) is another VGAM923 host target gene. APAF1 BINDING SITE1 and APAF1 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by APAF1, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APAF1 BINDING SITE1 and APAF1 BINDING SITE2, designated SEQ ID:14866 and SEQ ID:6827 respectively, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34797] Another function of VGAM923 is therefore inhibition of Apoptotic Protease Activating Factor (APAF1, Accession NM\_013229), a gene which functions in the mitochondrial apoptotic pathway that leads to caspase 9 dependent activation of caspase 3. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APAF1. The function of APAF1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM552. Coronin, Actin Binding Protein, 2B (CORO2B,

Accession XM\_035403) is another VGAM923 host target gene. CORO2B BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by CORO2B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CORO2B BINDING SITE, designated SEQ ID:32252, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34798] Another function of VGAM923 is therefore inhibition of Coronin, Actin Binding Protein, 2B (CORO2B, Accession XM\_035403), a gene which may play a role in the reorganization of neuronal actin structure. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CORO2B. The function of CORO2B has been established by previous studies. The Dictyostelium actin-binding protein coronin accumulates at the leading edges of motile cells and in crown-shaped extensions on the dorsal cell surface. Coronin is involved in cell motility, cytokinesis, and phagocytosis, all of which depend on cytoskeletal rearrangement; see CORO1A (OMIM Ref. No. 605000). By

screening a frontal cortex cDNA library with a brain-enriched clone showing similarity to Dictyostelium coronin, Nakamura et al. (1999) isolated a full-length cDNA encoding CORO2B, which they called CLIPINC. The predicted 475-amino acid CORO2B protein has an N-terminal domain containing 5 WD repeats and a succeeding domain with a tendency to form alpha helices. Northern blot analysis detected abundant expression of an approximately 4.0-kb CORO2B transcript in brain, with moderate expression in heart and ovary, and little or no expression in other tissues tested. In contrast, CORO1A is primarily expressed in immune system tissues, and CORO2A (OMIM Ref. No. 602159) is predominantly expressed in colon, prostate, and testis. Immunohistochemical analysis revealed Coro2a expression in mouse cerebral cortex, hippocampus, thalamus, olfactory bulb, and cerebellum, as well as in the inner nuclear layer of embryonic retina and embryonic olfactory bulb. Cosedimentation analysis demonstrated that CORO2B associates with F-actin. Immunofluorescence analysis indicated that CORO2B accumulates at neurite tips, at focal adhesions in association with VCL (OMIM Ref. No. 193065), and along stress fibers.

[34799] Full details of the abovementioned studies are described

in the following publications, the disclosure of which are hereby incorporated by reference:

- [34800] Nagase, T.; Ishikawa, K.; Suyama, M.; Kikuno, R.; Hiro-sawa, M.; Miyajima, N.; Tanaka, A.; Kotani, H.; Nomura, N.; Ohara, O. : Prediction of the coding sequences of unidentified human genes. XIII. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. DNA Res. 6: 63–70, 1999. ; and
- [34801] Nakamura, T.; Takeuchi, K.; Muraoka, S.; Takezoe, H.; Takahashi, N.; Mori, N. : A neurally enriched coronin-like protein, ClipnC, is a novel candidate for an actin cytoskeleton-cortical.
- [34802] Further studies establishing the function and utilities of CORO2B are found in John Hopkins OMIM database record ID 605002, and in cited publications numbered 8593 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Cytochrome P450, Subfamily VIIIB (sterol 12- $\alpha$ -hydroxylase), Polypeptide 1 (CYP8B1, Accession NM\_004391) is another VGAM923 host target gene. CYP8B1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CYP8B1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CYP8B1 BINDING SITE, designated SEQ ID:10619, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34803] Another function of VGAM923 is therefore inhibition of Cytochrome P450, Subfamily VIII B (sterol 12- $\alpha$ -hydroxylase), Polypeptide 1 (CYP8B1, Accession NM\_004391), a gene which functions in bile acid biosynthesis. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CYP8B1. The function of CYP8B1 has been established by previous studies. Zhang and Chiang (2001) showed that hepatocyte nuclear factor-4- $\alpha$  (HNF4A; 600281) strongly activates CYP8B1 promoter activity, whereas CYP7A promoter-binding factor (CPF, or NR5A2; 604453) has much less effect. The promoter activities were strongly repressed by bile acid. EMSA and site-directed mutagenesis analysis indicated that HNF4A, CPF, and the bile acid response element have overlapping binding sites in CYP8B1. Mammalian 2-hybrid analysis demonstrated interaction of HNF4A with the small heterodimer partner (SHP; 604630). Functional analysis

determined that SHP represses HNF4A-induced CYP8B1 transcription. Zhang and Chiang (2001) concluded that bile acids repress human CYP8B1 transcription by reducing the transactivation activity of HNF4A through the interaction of HNF4A with SHP and a reduction of HNF4A expression in liver. Gafvels et al. (1999) obtained cDNAs encoding human and mouse CYP8B1. The deduced 501-amino acid human CYP8B1 protein is approximately 75% identical to the mouse and rabbit proteins. It contains a hydrophobic, membrane-spanning N terminus and conserved oxygen-binding, steroidogenic, and heme-binding segments. Northern blot analysis revealed expression of a 3.9-kb CYP8B1 transcript in liver. In mouse, expression was restricted to liver.

[34804] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34805] Gafvels, M.; Olin, M.; Chowdhary, B. P.; Raudsepp, T.; Andersson, U.; Persson, B.; Jansson, M.; Bjorkhem, I.; Eggertsen, G. : Structure and chromosomal assignment of the sterol 12- $\alpha$ -hydroxylase gene (CYP8B1) in human and mouse: eukaryotic cytochrome P-450 gene devoid of introns. *Genomics* 56: 184-196, 1999. ; and

- [34806] Zhang, M.; Chiang, J. Y. L. : Transcriptional regulation of the human sterol 12- $\alpha$ -hydroxylase gene (CYP8B1): roles of hepatocyte nuclear factor 4- $\alpha$  in mediating bile acid repre.
- [34807] Further studies establishing the function and utilities of CYP8B1 are found in John Hopkins OMIM database record ID 602172, and in cited publications numbered 5994-5996 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Fc Fragment of IgA, Receptor For (FCAR, Accession NM\_133279) is another VGAM923 host target gene. FCAR BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FCAR, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FCAR BINDING SITE, designated SEQ ID:28432, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.
- [34808] Another function of VGAM923 is therefore inhibition of Fc Fragment of IgA, Receptor For (FCAR, Accession NM\_133279), a gene which binds to the fc region of immunoglobulins alpha and mediates several functions in-

cluding cytokine production. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FCAR. The function of FCAR has been established by previous studies. Human Fc-alpha receptor (FCAR) is present on a number of cell types, including neutrophils, monocytes, macrophages, and eosinophils. FCAR interacts with aggregated IgAs, such as IgA coated on the surface of an invading microorganism, and mediates several immunologic defense processes such as phagocytosis, antibody-dependent cell-mediated cytotoxicity, and stimulation of the release of inflammatory mediators. FCAR is a glycoprotein of 50 to 100 kD, with diversity on different cell types. Narita et al. (2001) examined polymorphisms in the promoter and 5-prime untranslated region of the FCAR gene in 151 patients with IgA nephropathy and 163 patients with other glomerular diseases shown to have no mesangial IgA deposition by renal biopsy. Haplotype analysis showed tight linkage disequilibrium among the polymorphisms. No significant association for the genotype, allele, and haplotype frequencies of the polymorphisms were shown between the patients with histologically proven IgA nephropathy and those with other glomerular diseases.



Thus, the analyzed polymorphisms did not appear to be primarily involved in susceptibility to IgA nephropathy.

[34809] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34810] Narita, I.; Goto, S.; Saito, N.; Sakatsume, M.; Jin, S.; Omori, K.; Gejyo, F. : Genetic polymorphisms in the promoter and 5-prime UTR region of the Fc alpha receptor (CD89) are not associated with a risk of IgA nephropathy. J. Hum. Genet. 46: 694–698, 2001. ; and

[34811] Maliszewski, C. R.; March, C. J.; Schoenborn, M. A.; Gimpel, S.; Shen, L. : Expression cloning of a human Fc receptor for IgA. J. Exp. Med. 172: 1665–1672, 1990.

[34812] Further studies establishing the function and utilities of FCAR are found in John Hopkins OMIM database record ID 147045, and in cited publications numbered 3162–3164, 3158–316 and 3165–3166 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. GM2 Ganglioside Activator Protein (GM2A, Accession XM\_041978) is another VGAM923 host target gene. GM2A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GM2A, corresponding to a HOST TARGET binding site

such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GM2A BINDING SITE, designated SEQ ID:33656, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34813] Another function of VGAM923 is therefore inhibition of GM2 Ganglioside Activator Protein (GM2A, Accession XM\_041978). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GM2A. G Protein-coupled Receptor 81 (GPR81, Accession NM\_032554) is another VGAM923 host target gene. GPR81 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by GPR81, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of GPR81 BINDING SITE, designated SEQ ID:26278, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34814] Another function of VGAM923 is therefore inhibition of G Protein-coupled Receptor 81 (GPR81, Accession

NM\_032554). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GPR81. HCS (Accession NM\_018947) is another VGAM923 host target gene. HCS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by HCS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HCS BINDING SITE, designated SEQ ID:21013, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34815] Another function of VGAM923 is therefore inhibition of HCS (Accession NM\_018947). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HCS. Interleukin 11 (IL11, Accession NM\_000641) is another VGAM923 host target gene. IL11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by IL11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of IL11 BINDING SITE, desig-

nated SEQ ID:6277, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34816] Another function of VGAM923 is therefore inhibition of Interleukin 11 (IL11, Accession NM\_000641), a gene which stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with IL11. The function of IL11 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM178. NAD(P)H Dehydrogenase, Quinone 1 (NQO1, Accession NM\_000903) is another VGAM923 host target gene. NQO1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NQO1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NQO1 BINDING SITE, designated SEQ ID:6605, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ

ID:3634.

[34817] Another function of VGAM923 is therefore inhibition of NAD(P)H Dehydrogenase, Quinone 1 (NQO1, Accession NM\_000903), a gene which is cytochrome b5 reductase which reduces redox dyes and quinones. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NQO1. The function of NQO1 has been established by previous studies. By study of man–mouse somatic cell hybrids, Grzeschik (1980) and Povey et al. (1980) identified a fourth diaphorase locus (DIA4) which segregates with chromosome 16. The regional assignment was 16q12–q22 (smallest region of overlap, SRO). Edwards et al. (1983) showed that the quantitative polymorphism of DIA4 can be attributed to the segregation of a 'low activity' allele. In 4 to 6% of persons there is a DIA4–absent phenotype. In a series of human/hamster hybrids, made using a human parental cell heterozygous for both phosphoglycolate phosphatase (PGP; 172280) and DIA4, the low activity allele and the PGP(2) allele cosegregated except in 2 of 16 discordant hybrids. DIA4 is presumably the same as NAD(P)H:menadione oxidoreductase (NMOR1). Jaiswal et al. (1988) showed that tetrachlorodibenzo–

p-dioxin (TCDD) treatment of a human hepatoblastoma cell produced a 5-fold induction of NMOR1 activity. They isolated several overlapping human NMOR1 cDNAs.

Southern blot analysis of human genomic DNA suggested the presence of a single NMOR1 gene approximately 10 kb long. They identified 4 potential polyadenylation sites and found 3 mRNAs in human cells. The 3 mRNA species appeared to be differentially regulated following TCDD treatment. By means of Southern blot analysis of genomic DNA from human/rodent somatic cell hybrids, Jaiswal et al. (1988) demonstrated that the gene is located on chromosome 16, consistent with the assignment of DIA4 to that chromosome. By means of mouse/human somatic cell hybrids containing rearranged chromosome 16 together with multiple probes, Chen et al. (1991) assigned the NMOR1 locus to 16q22.1. Animal model experiments lend further support to the function of NQO1. Radjendirane et al. (1998) generated Nqo1-null mice by targeted disruption. Mice lacking NQO1 gene expression were indistinguishable from wildtype mice. However, Nqo1-null mice exhibited increased toxicity when administered menadione compared with wildtype mice. These results established a role for NQO1 in protection against quinone

toxicity.

- [34818] It is appreciated that the abovementioned animal model for NQO1 is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.
- [34819] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:
- [34820] Jaiswal, A. K.; McBride, O. W.; Adesnik, M.; Nebert, D. W. : Human dioxin-inducible cytosolic NAD(P)H:menadione oxidoreductase: cDNA sequence and localization of gene to chromosome 16. J. Biol. Chem. 263: 13572–13578, 1988. ; and
- [34821] Radjendirane, V.; Joseph, P.; Lee, Y.-H.; Kimura, S.; Klein-Szanto, A. J. P.; Gonzalez, F. J.; Jaiswal, A. K. : Disruption of the DT diaphorase (NQO1) gene in mice leads to increased me.
- [34822] Further studies establishing the function and utilities of NQO1 are found in John Hopkins OMIM database record ID 125860, and in cited publications numbered 11858–11867, 1187 and 11868–11872 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Phosphoribosylaminoimidazole Car-

boxylase, Phosphoribosylaminoimidazole Succinocarboxamide Synthetase (PAICS, Accession NM\_006452) is another VGAM923 host target gene. PAICS BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PAICS, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PAICS BINDING SITE, designated SEQ ID:13161, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34823] Another function of VGAM923 is therefore inhibition of Phosphoribosylaminoimidazole Carboxylase, Phosphoribosylaminoimidazole Succinocarboxamide Synthetase (PAICS, Accession NM\_006452), a gene which is required for purine biosynthesis. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PAICS. The function of PAICS and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM894. Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005) is another VGAM923 host target gene.



PCDHA9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PCDHA9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PCDHA9 BINDING SITE, designated SEQ ID:15206, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34824] Another function of VGAM923 is therefore inhibition of Protocadherin Alpha 9 (PCDHA9, Accession NM\_014005), a gene which is a calcium-dependent cell-adhesion protein. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PCDHA9. The function of PCDHA9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM71. Phosphoinositide-3-kinase, Class 2, Beta Polypeptide (PIK3C2B, Accession NM\_002646) is another VGAM923 host target gene. PIK3C2B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PIK3C2B, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PIK3C2B BINDING SITE, designated SEQ ID:8503, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34825] Another function of VGAM923 is therefore inhibition of Phosphoinositide-3-kinase, Class 2, Beta Polypeptide (PIK3C2B, Accession NM\_002646). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PIK3C2B. Rhesus Blood Group, D Antigen (RHD, Accession NM\_016124) is another VGAM923 host target gene. RHD BINDING SITE1 and RHD BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by RHD, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of RHD BINDING SITE1 and RHD BINDING SITE2, designated SEQ ID:18213 and SEQ ID:18333 respectively, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34826] Another function of VGAM923 is therefore inhibition of Rhesus Blood Group, D Antigen (RHD, Accession NM\_016124), a gene which Major antigen of the RH system. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with RHD. The function of RHD and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74. Sex Comb On Midleg-like 2 (Drosophila) (SCML2, Accession NM\_006089) is another VGAM923 host target gene. SCML2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SCML2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SCML2 BINDING SITE, designated SEQ ID:12734, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34827] Another function of VGAM923 is therefore inhibition of Sex Comb On Midleg-like 2 (Drosophila) (SCML2, Accession NM\_006089). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and

clinical conditions associated with SCML2. Spondyloepiphyseal Dysplasia, Late (SEDL, Accession NM\_014563) is another VGAM923 host target gene. SEDL BINDING SITE1 through SEDL BINDING SITE3 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by SEDL, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SEDL BINDING SITE1 through SEDL BINDING SITE3, designated SEQ ID:15900, SEQ ID:15901 and SEQ ID:15899 respectively, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34828] Another function of VGAM923 is therefore inhibition of Spondyloepiphyseal Dysplasia, Late (SEDL, Accession NM\_014563), a gene which may play role in vesicular transport from endoplasmic reticulum to golgi. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SEDL. The function of SEDL and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM74. Serine (or cysteine) Proteinase

Inhibitor, Clade B (ovalbumin), Member 9 (SERPINB9, Accession NM\_004155) is another VGAM923 host target gene. SERPINB9 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SERPINB9, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SERPINB9 BINDING SITE, designated SEQ ID:10357, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34829] Another function of VGAM923 is therefore inhibition of Serine (or cysteine) Proteinase Inhibitor, Clade B (ovalbumin), Member 9 (SERPINB9, Accession NM\_004155), a gene which may be a serpin serine protease inhibitor that interacts with granzyme B (GZMB). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SERPINB9. The function of SERPINB9 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM60.Solute Carrier Family 24 (sodium/potassium/calcium exchanger), Mem-

ber 1 (SLC24A1, Accession NM\_004727) is another VGAM923 host target gene. SLC24A1 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC24A1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC24A1 BINDING SITE, designated SEQ ID:11099, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34830] Another function of VGAM923 is therefore inhibition of Solute Carrier Family 24 (sodium/potassium/calcium exchanger), Member 1 (SLC24A1, Accession NM\_004727), a gene which is a critical component of the visual transduction cascade, controlling the calcium concentration of outer segments during light and darkness. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC24A1. The function of SLC24A1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM142. Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Ac-

cession NM\_003842) is another VGAM923 host target gene. TNFRSF10B BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by TNFRSF10B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TNFRSF10B BINDING SITE, designated SEQ ID:9933, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34831] Another function of VGAM923 is therefore inhibition of Tumor Necrosis Factor Receptor Superfamily, Member 10b (TNFRSF10B, Accession NM\_003842), a gene which forms complex that induces apoptosis. Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TNFRSF10B. The function of TNFRSF10B and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM400. AAK1 (Accession NM\_014911) is another VGAM923 host target gene. AAK1 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by AAK1, corresponding to a

HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of AAK1 BINDING SITE, designated SEQ ID:17143, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34832] Another function of VGAM923 is therefore inhibition of AAK1 (Accession NM\_014911). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with AAK1. ADMP (Accession NM\_145035) is another VGAM923 host target gene. ADMP BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADMP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADMP BINDING SITE, designated SEQ ID:29658, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34833] Another function of VGAM923 is therefore inhibition of ADMP (Accession NM\_145035). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of



diseases and clinical conditions associated with ADMP. Ankyrin Repeat and SOCS Box-containing 16 (ASB16, Accession XM\_046024) is another VGAM923 host target gene. ASB16 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by ASB16, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ASB16 BINDING SITE, designated SEQ ID:34652, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34834] Another function of VGAM923 is therefore inhibition of Ankyrin Repeat and SOCS Box-containing 16 (ASB16, Accession XM\_046024). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ASB16. Chromosome 1 Open Reading Frame 34 (C1orf34, Accession XM\_027172) is another VGAM923 host target gene. C1orf34 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by C1orf34, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of C1orf34 BINDING SITE, designated SEQ ID:30433, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34835] Another function of VGAM923 is therefore inhibition of Chromosome 1 Open Reading Frame 34 (C1orf34, Accession XM\_027172). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with C1orf34. CIP29 (Accession NM\_032364) is another VGAM923 host target gene. CIP29 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by CIP29, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CIP29 BINDING SITE, designated SEQ ID:26147, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34836] Another function of VGAM923 is therefore inhibition of CIP29 (Accession NM\_032364). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CIP29.

DKFZp434C0923 (Accession NM\_017598) is another VGAM923 host target gene. DKFZp434C0923 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZp434C0923, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZp434C0923 BINDING SITE, designated SEQ ID:19061, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34837] Another function of VGAM923 is therefore inhibition of DKFZp434C0923 (Accession NM\_017598). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZp434C0923. DKFZP566I1024 (Accession XM\_046506) is another VGAM923 host target gene. DKFZP566I1024 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by DKFZP566I1024, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DKFZP566I1024 BINDING SITE,

designated SEQ ID:34733, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34838] Another function of VGAM923 is therefore inhibition of DKFZP566I1024 (Accession XM\_046506). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DKFZP566I1024. FLJ10535 (Accession NM\_018129) is another VGAM923 host target gene. FLJ10535 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ10535, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10535 BINDING SITE, designated SEQ ID:19915, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34839] Another function of VGAM923 is therefore inhibition of FLJ10535 (Accession NM\_018129). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10535. FLJ10956 (Accession NM\_018283) is another VGAM923 host target gene. FLJ10956 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by FLJ10956, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ10956 BINDING SITE, designated SEQ ID:20274, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34840] Another function of VGAM923 is therefore inhibition of FLJ10956 (Accession NM\_018283). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ10956. FLJ13072 (Accession XM\_117117) is another VGAM923 host target gene. FLJ13072 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FLJ13072, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13072 BINDING SITE, designated SEQ ID:43231, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34841] Another function of VGAM923 is therefore inhibition of

FLJ13072 (Accession XM\_117117). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13072. FLJ13952 (Accession NM\_024798) is another VGAM923 host target gene. FLJ13952 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ13952, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ13952 BINDING SITE, designated SEQ ID:24175, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34842] Another function of VGAM923 is therefore inhibition of FLJ13952 (Accession NM\_024798). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ13952. FLJ14803 (Accession NM\_032842) is another VGAM923 host target gene. FLJ14803 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ14803, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity

of the nucleotide sequences of FLJ14803 BINDING SITE, designated SEQ ID:26624, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34843] Another function of VGAM923 is therefore inhibition of FLJ14803 (Accession NM\_032842). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ14803. FLJ20045 (Accession NM\_017638) is another VGAM923 host target gene. FLJ20045 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20045, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20045 BINDING SITE, designated SEQ ID:19143, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34844] Another function of VGAM923 is therefore inhibition of FLJ20045 (Accession NM\_017638). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20045. FLJ20671 (Accession NM\_017924) is another VGAM923

host target gene. FLJ20671 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ20671, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ20671 BINDING SITE, designated SEQ ID:19590, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34845] Another function of VGAM923 is therefore inhibition of FLJ20671 (Accession NM\_017924). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ20671. FLJ22969 (Accession XM\_044006) is another VGAM923 host target gene. FLJ22969 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ22969, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22969 BINDING SITE, designated SEQ ID:34063, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.



[34846] Another function of VGAM923 is therefore inhibition of FLJ22969 (Accession XM\_044006). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22969. FLJ23356 (Accession NM\_032237) is another VGAM923 host target gene. FLJ23356 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by FLJ23356, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ23356 BINDING SITE, designated SEQ ID:25956, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34847] Another function of VGAM923 is therefore inhibition of FLJ23356 (Accession NM\_032237). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ23356. GR6 (Accession NM\_007354) is another VGAM923 host target gene. GR6 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by GR6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III.

Table 2 illustrates the complementarity of the nucleotide sequences of GR6 BINDING SITE, designated SEQ ID:14279, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34848] Another function of VGAM923 is therefore inhibition of GR6 (Accession NM\_007354). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with GR6. HSPC065 (Accession NM\_014157) is another VGAM923 host target gene. HSPC065 BINDING SITE1 and HSPC065 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by HSPC065, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HSPC065 BINDING SITE1 and HSPC065 BINDING SITE2, designated SEQ ID:15447 and SEQ ID:15448 respectively, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34849] Another function of VGAM923 is therefore inhibition of HSPC065 (Accession NM\_014157). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of

diseases and clinical conditions associated with HSPC065. KIAA0513 (Accession NM\_014732) is another VGAM923 host target gene. KIAA0513 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0513, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0513 BINDING SITE, designated SEQ ID:16350, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34850] Another function of VGAM923 is therefore inhibition of KIAA0513 (Accession NM\_014732). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0513. KIAA0527 (Accession XM\_171054) is another VGAM923 host target gene. KIAA0527 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0527, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0527 BINDING SITE, designated SEQ ID:45839, to the

nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34851] Another function of VGAM923 is therefore inhibition of KIAA0527 (Accession XM\_171054). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0527. KIAA1041 (Accession NM\_014947) is another VGAM923 host target gene. KIAA1041 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1041, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1041 BINDING SITE, designated SEQ ID:17262, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34852] Another function of VGAM923 is therefore inhibition of KIAA1041 (Accession NM\_014947). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1041. KIAA1198 (Accession XM\_032674) is another VGAM923 host target gene. KIAA1198 BINDING SITE is HOST TARGET binding site found in the 3' untranslated

region of mRNA encoded by KIAA1198, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1198 BINDING SITE, designated SEQ ID:31700, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34853] Another function of VGAM923 is therefore inhibition of KIAA1198 (Accession XM\_032674). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1198. KIAA1200 (Accession XM\_031054) is another VGAM923 host target gene. KIAA1200 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1200, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1200 BINDING SITE, designated SEQ ID:31261, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34854] Another function of VGAM923 is therefore inhibition of KIAA1200 (Accession XM\_031054). Accordingly, utilities

of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1200. KIAA1257 (Accession XM\_031577) is another VGAM923 host target gene. KIAA1257 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1257, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1257 BINDING SITE, designated SEQ ID:31427, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34855] Another function of VGAM923 is therefore inhibition of KIAA1257 (Accession XM\_031577). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1257. KIAA1655 (Accession XM\_039442) is another VGAM923 host target gene. KIAA1655 BINDING SITE1 and KIAA1655 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by KIAA1655, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide

sequences of KIAA1655 BINDING SITE1 and KIAA1655 BINDING SITE2, designated SEQ ID:33079 and SEQ ID:33080 respectively, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34856] Another function of VGAM923 is therefore inhibition of KIAA1655 (Accession XM\_039442). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1655. KIAA1878 (Accession XM\_166256) is another VGAM923 host target gene. KIAA1878 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1878, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1878 BINDING SITE, designated SEQ ID:44073, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34857] Another function of VGAM923 is therefore inhibition of KIAA1878 (Accession XM\_166256). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with

KIAA1878. MGC13138 (Accession NM\_033410) is another VGAM923 host target gene. MGC13138 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by MGC13138, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC13138 BINDING SITE, designated SEQ ID:27231, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34858] Another function of VGAM923 is therefore inhibition of MGC13138 (Accession NM\_033410). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC13138. MGC15606 (Accession NM\_145037) is another VGAM923 host target gene. MGC15606 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by MGC15606, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of MGC15606 BINDING SITE, designated SEQ ID:29660, to the nucleotide sequence of VGAM923 RNA, herein desig-



nated VGAM RNA, also designated SEQ ID:3634.

[34859] Another function of VGAM923 is therefore inhibition of MGC15606 (Accession NM\_145037). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MGC15606. NADH Dehydrogenase (ubiquinone) 1, Sub-complex Unknown, 2, 14.5kDa (NDUFC2, Accession NM\_004549) is another VGAM923 host target gene. NDUFC2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by NDUFC2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of NDUFC2 BINDING SITE, designated SEQ ID:10893, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34860] Another function of VGAM923 is therefore inhibition of NADH Dehydrogenase (ubiquinone) 1, Subcomplex Unknown, 2, 14.5kDa (NDUFC2, Accession NM\_004549). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with NDUFC2. PP1201 (Accession NM\_022152) is

another VGAM923 host target gene. PP1201 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PP1201, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PP1201 BINDING SITE, designated SEQ ID:22710, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34861] Another function of VGAM923 is therefore inhibition of PP1201 (Accession NM\_022152). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PP1201. Solute Carrier Family 11 (proton-coupled divalent metal ion transporters), Member 2 (SLC11A2, Accession NM\_000617) is another VGAM923 host target gene. SLC11A2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC11A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC11A2 BINDING SITE, designated SEQ ID:6220, to the nucleotide sequence of VGAM923 RNA,

herein designated VGAM RNA, also designated SEQ ID:3634.

[34862] Another function of VGAM923 is therefore inhibition of Solute Carrier Family 11 (proton-coupled divalent metal ion transporters), Member 2 (SLC11A2, Accession NM\_000617). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC11A2. Solute Carrier Family 12 (potassium/chloride transporters), Member 8 (SLC12A8, Accession NM\_024628) is another VGAM923 host target gene. SLC12A8 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SLC12A8, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC12A8 BINDING SITE, designated SEQ ID:23892, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34863] Another function of VGAM923 is therefore inhibition of Solute Carrier Family 12 (potassium/chloride transporters), Member 8 (SLC12A8, Accession NM\_024628). Accordingly, utilities of VGAM923 include diagnosis, pre-

vention and treatment of diseases and clinical conditions associated with SLC12A8. Tripartite Motif-containing 16 (TRIM16, Accession NM\_006470) is another VGAM923 host target gene. TRIM16 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM16, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of TRIM16 BINDING SITE, designated SEQ ID:13194, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34864] Another function of VGAM923 is therefore inhibition of Tripartite Motif-containing 16 (TRIM16, Accession NM\_006470). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM16. Tripartite Motif-containing 5 (TRIM5, Accession NM\_033034) is another VGAM923 host target gene. TRIM5 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by TRIM5, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complemen-

tarity of the nucleotide sequences of TRIM5 BINDING SITE, designated SEQ ID:26926, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34865] Another function of VGAM923 is therefore inhibition of Tripartite Motif-containing 5 (TRIM5, Accession NM\_033034). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with TRIM5. Vacuolar Protein Sorting 33A (yeast) (VPS33A, Accession NM\_022916) is another VGAM923 host target gene. VPS33A BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by VPS33A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of VPS33A BINDING SITE, designated SEQ ID:23230, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34866] Another function of VGAM923 is therefore inhibition of Vacuolar Protein Sorting 33A (yeast) (VPS33A, Accession NM\_022916). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical

cal conditions associated with VPS33A. LOC119392 (Accession NM\_145247) is another VGAM923 host target gene. LOC119392 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC119392, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC119392 BINDING SITE, designated SEQ ID:29758, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34867] Another function of VGAM923 is therefore inhibition of LOC119392 (Accession NM\_145247). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC119392. LOC128989 (Accession XM\_059310) is another VGAM923 host target gene. LOC128989 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC128989, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC128989 BINDING SITE, designated SEQ ID:36938, to

the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34868] Another function of VGAM923 is therefore inhibition of LOC128989 (Accession XM\_059310). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC128989. LOC135154 (Accession XM\_059752) is another VGAM923 host target gene. LOC135154 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC135154, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC135154 BINDING SITE, designated SEQ ID:37090, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34869] Another function of VGAM923 is therefore inhibition of LOC135154 (Accession XM\_059752). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC135154. LOC147166 (Accession XM\_085722) is another VGAM923 host target gene. LOC147166 BINDING SITE is HOST TARGET binding site found in the 3' un-

translated region of mRNA encoded by LOC147166, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147166 BINDING SITE, designated SEQ ID:38312, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34870] Another function of VGAM923 is therefore inhibition of LOC147166 (Accession XM\_085722). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147166. LOC148195 (Accession XM\_097419) is another VGAM923 host target gene. LOC148195 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC148195, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC148195 BINDING SITE, designated SEQ ID:40870, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34871] Another function of VGAM923 is therefore inhibition of LOC148195 (Accession XM\_097419). Accordingly, utilities



of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC148195. LOC149577 (Accession XM\_097675) is another VGAM923 host target gene. LOC149577 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC149577, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC149577 BINDING SITE, designated SEQ ID:41020, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34872] Another function of VGAM923 is therefore inhibition of LOC149577 (Accession XM\_097675). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC149577. LOC152343 (Accession XM\_087441) is another VGAM923 host target gene. LOC152343 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC152343, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC152343 BINDING SITE, designated SEQ ID:39259, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34873] Another function of VGAM923 is therefore inhibition of LOC152343 (Accession XM\_087441). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152343. LOC152620 (Accession XM\_011108) is another VGAM923 host target gene. LOC152620 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC152620, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152620 BINDING SITE, designated SEQ ID:30170, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34874] Another function of VGAM923 is therefore inhibition of LOC152620 (Accession XM\_011108). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152620. LOC152719 (Accession XM\_098257) is another VGAM923 host target gene. LOC152719 BINDING

SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC152719, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC152719 BINDING SITE, designated SEQ ID:41542, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34875] Another function of VGAM923 is therefore inhibition of LOC152719 (Accession XM\_098257). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC152719. LOC158476 (Accession XM\_098955) is another VGAM923 host target gene. LOC158476 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by LOC158476, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158476 BINDING SITE, designated SEQ ID:41993, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34876] Another function of VGAM923 is therefore inhibition of

LOC158476 (Accession XM\_098955). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158476. LOC158549 (Accession XM\_098963) is another VGAM923 host target gene. LOC158549 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC158549, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC158549 BINDING SITE, designated SEQ ID:42003, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34877] Another function of VGAM923 is therefore inhibition of LOC158549 (Accession XM\_098963). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC158549. LOC161829 (Accession XM\_091161) is another VGAM923 host target gene. LOC161829 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC161829, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 il-

illustrates the complementarity of the nucleotide sequences of LOC161829 BINDING SITE, designated SEQ ID:40035, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34878] Another function of VGAM923 is therefore inhibition of LOC161829 (Accession XM\_091161). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC161829. LOC163590 (Accession NM\_145034) is another VGAM923 host target gene. LOC163590 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC163590, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC163590 BINDING SITE, designated SEQ ID:29651, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34879] Another function of VGAM923 is therefore inhibition of LOC163590 (Accession NM\_145034). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC163590. LOC202025 (Accession XM\_117353) is an-

other VGAM923 host target gene. LOC202025 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202025, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202025 BINDING SITE, designated SEQ ID:43398, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34880] Another function of VGAM923 is therefore inhibition of LOC202025 (Accession XM\_117353). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202025. LOC202908 (Accession XM\_114602) is another VGAM923 host target gene. LOC202908 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC202908, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202908 BINDING SITE, designated SEQ ID:42993, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34881] Another function of VGAM923 is therefore inhibition of LOC202908 (Accession XM\_114602). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202908. LOC202934 (Accession XM\_117486) is another VGAM923 host target gene. LOC202934 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC202934, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC202934 BINDING SITE, designated SEQ ID:43451, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34882] Another function of VGAM923 is therefore inhibition of LOC202934 (Accession XM\_117486). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC202934. LOC220662 (Accession XM\_165978) is another VGAM923 host target gene. LOC220662 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC220662, corresponding to a HOST TARGET binding site such as BIND-

ING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC220662 BINDING SITE, designated SEQ ID:43820, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34883] Another function of VGAM923 is therefore inhibition of LOC220662 (Accession XM\_165978). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC220662. LOC222070 (Accession XM\_168433) is another VGAM923 host target gene. LOC222070 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC222070, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC222070 BINDING SITE, designated SEQ ID:45175, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34884] Another function of VGAM923 is therefore inhibition of LOC222070 (Accession XM\_168433). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with



LOC222070. LOC256306 (Accession XM\_172976) is another VGAM923 host target gene. LOC256306 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC256306, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC256306 BINDING SITE, designated SEQ ID:46233, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34885] Another function of VGAM923 is therefore inhibition of LOC256306 (Accession XM\_172976). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC256306. LOC51200 (Accession NM\_016352) is another VGAM923 host target gene. LOC51200 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LOC51200, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51200 BINDING SITE, designated SEQ ID:18478, to the nucleotide sequence of VGAM923 RNA, herein designated

VGAM RNA, also designated SEQ ID:3634.

[34886] Another function of VGAM923 is therefore inhibition of LOC51200 (Accession NM\_016352). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51200. LOC51219 (Accession NM\_016418) is another VGAM923 host target gene. LOC51219 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC51219, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC51219 BINDING SITE, designated SEQ ID:18543, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34887] Another function of VGAM923 is therefore inhibition of LOC51219 (Accession NM\_016418). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC51219. LOC90333 (Accession XM\_030958) is another VGAM923 host target gene. LOC90333 BINDING SITE1 and LOC90333 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by

LOC90333, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90333 BINDING SITE1 and LOC90333 BINDING SITE2, designated SEQ ID:31215 and SEQ ID:31216 respectively, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34888] Another function of VGAM923 is therefore inhibition of LOC90333 (Accession XM\_030958). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90333. LOC93408 (Accession NM\_138403) is another VGAM923 host target gene. LOC93408 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC93408, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93408 BINDING SITE, designated SEQ ID:28772, to the nucleotide sequence of VGAM923 RNA, herein designated VGAM RNA, also designated SEQ ID:3634.

[34889] Another function of VGAM923 is therefore inhibition of

LOC93408 (Accession NM\_138403). Accordingly, utilities of VGAM923 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93408. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 924 (VGAM924) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34890] VGAM924 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM924 was detected is described hereinabove with reference to Figs. 1–8.

[34891] VGAM924 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Infectious Spleen and Kidney Necrosis Virus. VGAM924 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34892] VGAM924 gene encodes a VGAM924 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM924 precursor RNA does not encode a protein. A nucleotide

sequence identical or highly similar to the nucleotide sequence of VGAM924 precursor RNA is designated SEQ ID:910, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:910 is located at position 67724 relative to the genome of Infectious Spleen and Kidney Necrosis Virus.

[34893] VGAM924 precursor RNA folds onto itself, forming VGAM924 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34894] An enzyme complex designated DICER COMPLEX, `dices` the VGAM924 folded precursor RNA into VGAM924 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 42%) nucleotide se-

quence of VGAM924 RNA is designated SEQ ID:3635, and is provided hereinbelow with reference to the sequence listing part.

[34895] VGAM924 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM924 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM924 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5' untranslated region, a protein coding region and a 3' untranslated region, designated 5'UTR, PROTEIN CODING and 3'UTR respectively.

[34896] VGAM924 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM924 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM924 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is

meant as an illustration only, and is not meant to be limiting – VGAM924 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM924 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3'UTR region, this is meant as an example only – these host target binding sites may be located in the 3'UTR region, the 5'UTR region, or in both 3'UTR and 5'UTR regions.

[34897] The complementary binding of VGAM924 RNA, herein designated VGAM RNA, to host target binding sites on VGAM924 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM924 host target RNA into VGAM924 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34898] It is appreciated that VGAM924 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM924 host target genes. The mRNA of each one of this plurality of VGAM924 host target genes comprises one or more host target binding sites, each

having a nucleotide sequence which is at least partly complementary to VGAM924 RNA, herein designated VGAM RNA, and which when bound by VGAM924 RNA causes inhibition of translation of respective one or more VGAM924 host target proteins.

[34899] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM924 gene, herein designated VGAM GENE, on one or more VGAM924 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34900] It is yet further appreciated that a function of VGAM924 is



inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM924 include diagnosis, prevention and treatment of viral infection by Infectious Spleen and Kidney Necrosis Virus. Specific functions, and accordingly utilities, of VGAM924 correlate with, and may be deduced from, the identity of the host target genes which VGAM924 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34901] Nucleotide sequences of the VGAM924 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM924 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM924 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM924 are further described hereinbelow with reference to Table 1.

[34902] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM924 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM924 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34903] As mentioned hereinabove with reference to Fig. 1, a function of VGAM924 gene, herein designated VGAM is inhibition of expression of VGAM924 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM924 correlate with, and may be deduced from, the identity of the target genes which VGAM924 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34904] Splicing Factor, Arginine/serine-rich 11 (SFRS11, Accession NM\_004768) is a VGAM924 host target gene. SFRS11 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SFRS11, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SFRS11 BINDING SITE, designated SEQ ID:11159, to the nucleotide sequence of VGAM924 RNA, herein designated VGAM RNA, also designated SEQ ID:3635.

[34905] A function of VGAM924 is therefore inhibition of Splicing Factor, Arginine/serine-rich 11 (SFRS11, Accession NM\_004768). Accordingly, utilities of VGAM924 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SFRS11. LOC205251

(Accession XM\_119554) is another VGAM924 host target gene. LOC205251 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC205251, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC205251 BINDING SITE, designated SEQ ID:43592, to the nucleotide sequence of VGAM924 RNA, herein designated VGAM RNA, also designated SEQ ID:3635.

[34906] Another function of VGAM924 is therefore inhibition of LOC205251 (Accession XM\_119554). Accordingly, utilities of VGAM924 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC205251. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 925 (VGAM925) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34907] VGAM925 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The

method by which VGAM925 was detected is described hereinabove with reference to Figs. 1–8.

[34908] VGAM925 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Infectious Spleen and Kidney Necrosis Virus. VGAM925 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34909] VGAM925 gene encodes a VGAM925 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM925 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM925 precursor RNA is designated SEQ ID:911, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:911 is located at position 67920 relative to the genome of Infectious Spleen and Kidney Necrosis Virus.

[34910] VGAM925 precursor RNA folds onto itself, forming VGAM925 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence

of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34911] An enzyme complex designated DICER COMPLEX, `dices` the VGAM925 folded precursor RNA into VGAM925 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 40%) nucleotide sequence of VGAM925 RNA is designated SEQ ID:3636, and is provided hereinbelow with reference to the sequence listing part.

[34912] VGAM925 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM925 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM925 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34913] VGAM925 RNA, herein designated VGAM RNA, binds com-

plementarily to one or more host target binding sites located in untranslated regions of VGAM925 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM925 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM925 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM925 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[34914] The complementary binding of VGAM925 RNA, herein designated VGAM RNA, to host target binding sites on

VGAM925 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM925 host target RNA into VGAM925 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34915] It is appreciated that VGAM925 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM925 host target genes. The mRNA of each one of this plurality of VGAM925 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM925 RNA, herein designated VGAM RNA, and which when bound by VGAM925 RNA causes inhibition of translation of respective one or more VGAM925 host target proteins.

[34916] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM925 gene, herein designated VGAM GENE, on one or more VGAM925 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove

with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34917] It is yet further appreciated that a function of VGAM925 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of viral infection by Infectious Spleen and Kidney Necrosis Virus. Specific functions, and accordingly utilities, of VGAM925 correlate with, and may be deduced from, the identity of the host target genes which VGAM925 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34918] Nucleotide sequences of the VGAM925 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM925 RNA, herein designated VGAM RNA,



and a schematic representation of the secondary folding of VGAM925 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM925 are further described hereinbelow with reference to Table 1.

[34919] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM925 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM925 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34920] As mentioned hereinabove with reference to Fig. 1, a function of VGAM925 gene, herein designated VGAM is inhibition of expression of VGAM925 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM925 correlate with, and may be deduced from, the identity of the target genes which VGAM925 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34921] Amyloid Beta (A4) Precursor Protein-binding, Family A, Member 2 (X11-like) (APBA2, Accession NM\_005503) is a VGAM925 host target gene. APBA2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region

of mRNA encoded by APBA2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of APBA2 BINDING SITE, designated SEQ ID:12016, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34922] A function of VGAM925 is therefore inhibition of Amyloid Beta (A4) Precursor Protein-binding, Family A, Member 2 (X11-like) (APBA2, Accession NM\_005503), a gene which interacts with and stabilises the Alzheimer's disease amyloid precursor protein (APP) and inhibits production of proteolytic APP fragments. Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with APBA2. The function of APBA2 has been established by previous studies. The cytoplasmic domain of the Alzheimer disease locus amyloid protein precursor (APP; 104760) binds to 4 human phosphotyrosine-binding (PTB) proteins; see APBA1 (OMIM Ref. No. 602414). By use of a yeast 2-hybrid screening of a human brain cDNA library, McLoughlin and Miller (1996) identified 3 of these proteins: the human homolog of rat Fe65 (APBB1; 602709), an Fe65-like se-

quence (APBB2; 602710), and an X11-like sequence (APBA2). The human X11-like sequence is 83% identical to that encoded by the X11 gene (APBA1; 602414).

McLoughlin and Miller (1996) detected a phosphotyrosine-binding domain in the protein encoded by the X11-like clone. Using a radiation hybrid panel, Blanco et al. (1998) mapped the APBA2 gene to human chromosome 15, between markers WI-5590 (10.31 cR) and D15S144 (21.7 cR). In an interspecific backcross, using an SSCP-demonstrated polymorphism, they assigned the Apba2 gene to mouse chromosome 7. The location of the flanking markers suggested that Apba2 is a further addition to a gene segment conserved between mouse chromosome 7 and human 15q.

[34923] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34924] Blanco, G.; Irving, N. G.; Brown, S. D. M.; Miller, C. C. J.; McLoughlin, D. M. : Mapping of the human and murine X11-like genes (APBA2 and Apba2), the murine Fe65 gene (Apbb1), and the human Fe65-like gene (APBB2): genes encoding phosphotyrosine-binding domain proteins that interact with the Alzheimer's disease amyloid precursor

protein. Mammalian Genome 9: 473–475, 1998. ; and

[34925] McLoughlin, D. M.; Miller, C. C. J. : The intracellular cytoplasmic domain of the Alzheimer's disease amyloid precursor protein interacts with phosphotyrosine-binding domain proteins in.

[34926] Further studies establishing the function and utilities of APBA2 are found in John Hopkins OMIM database record ID 602712, and in cited publications numbered 101 and 1118 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference.DNA

(cytosine–5–)-methyltransferase 3 Alpha (DNMT3A, Accession NM\_022552) is another VGAM925 host target gene. DNMT3A BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DNMT3A, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNMT3A BINDING SITE, designated SEQ ID:22881, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34927] Another function of VGAM925 is therefore inhibition of DNA (cytosine–5–)-methyltransferase 3 Alpha (DNMT3A,

Accession NM\_022552), a gene which intervenes in de novo methylation of DNA. Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNMT3A. The function of DNMT3A has been established by previous studies. De novo methylation of genomic DNA is a developmentally regulated process that appears to play a pivotal role in regulation of genomic imprinting and X-chromosome inactivation in mammals. Aberrant de novo methylation of growth regulatory genes is associated with tumorigenesis in humans (Baylin et al., 1998). However, Lei et al. (1996) showed that de novo methylation persists in embryonic stem (ES) cells lacking Dnmt1 (OMIM Ref. No. 126375), which encodes the constitutive DNA methyltransferase 1, indicating the existence of independently encoded de novo methyltransferases. By a TBLASTN search of the dbEST database using full-length bacterial type II cytosine-5 methyltransferase sequences as queries, followed by isolation and sequencing of overlapping cDNA clones, Okano et al. (1998) identified 2 homologous genes in both human and mouse that contain the highly conserved cytosine-5 methyltransferase motifs. The mouse genes, termed Dnmt3a and Dnmt3b (OMIM Ref. No.

602900), show little sequence similarity to mouse Dnmt1 and Dnmt2 (OMIM Ref. No. 602478), and masc1 from *Ascobolus*. The Dnmt3a cDNA is 4,192 bp in length, encoding a protein of 908 amino acids. The human DNMT3A and DNMT3B cDNA are highly homologous to the mouse genes. Dnmt3a and Dnmt3b transcripts are abundantly expressed in undifferentiated embryonic stem cells. Okano et al. (1998) performed other experiments suggesting that Dnmt3a and Dnmt3b encode the long-sought de novo DNA methyltransferases. By FISH, Xie et al. (1999) mapped the DNMT3A gene to 2p23. Robertson et al. (1999) also mapped the DNMT3A gene to 2p23 using FISH. Animal model experiments lend further support to the function of DNMT3A. Okano et al. (1999) generated mice with targeted disruption of the Dnmt3a and Dnmt3b genes. Inactivation of both genes blocked de novo methylation in embryonic stem cells and early embryos but had no effect on maintenance of imprinted methylation patterns. Dnmt3a  $-/-$  mice developed to term and appeared to be normal at birth. However, most homozygous mutant mice became runted and died at about 4 weeks of age. In contrast, no viable Dnmt3b  $-/-$  mice were recovered at birth. Dissection of embryos at different stages of devel-

opment revealed that Dnmt3b  $-/-$  embryos had multiple developmental defects, including growth impairment and rostral neural tube defects with variable severity at later stages of development, though most of them appeared to develop normally before E9.5. Dnmt3a and Dnmt3b also exhibited nonoverlapping functions in development, with Dnmt3b specifically required for methylation of centromeric minor satellite repeats. These results indicated that both Dnmt3a and Dnmt3b are required for genomewide de novo methylation and are essential for mammalian development.

[34928] It is appreciated that the abovementioned animal model for DNMT3A is acknowledged by those skilled in the art as a scientifically valid animal model, as can be further appreciated from the publications cited hereinbelow.

[34929] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34930] Okano, M.; Xie, S.; Li, E. : Cloning and characterization of a family of novel mammalian DNA (cytosine-5) methyltransferases. (Letter) Nature Genet. 19: 219-220, 1998. ; and

[34931] Robertson, K. D.; Uzvolgyi, E.; Liang, G.; Talmadge, C.;

Sumegi, J.; Gonzales, F. A.; Jones, P. A. : The human DNA methyltransferases (DNMTs) 1, 3a and 3b: coordinate mRNA expression in.

[34932] Further studies establishing the function and utilities of DNMT3A are found in John Hopkins OMIM database record ID 602769, and in cited publications numbered 6213–6214, 344 and 11685–6217 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. DNA (cytosine–5–)-methyltransferase 3–like (DNMT3L, Accession NM\_013369) is another VGAM925 host target gene. DNMT3L BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by DNMT3L, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of DNMT3L BINDING SITE, designated SEQ ID:15016, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34933] Another function of VGAM925 is therefore inhibition of DNA (cytosine–5–)-methyltransferase 3–like (DNMT3L, Accession NM\_013369), a gene which plays a role in de novo methylation of CpG islands. Accordingly, utilities of



VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with DNMT3L. The function of DNMT3L and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM447. Fibroblast Growth Factor 18 (FGF18, Accession NM\_033649) is another VGAM925 host target gene. FGF18 BINDING SITE1 and FGF18 BINDING SITE2 are HOST TARGET binding sites found in untranslated regions of mRNA encoded by FGF18, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FGF18 BINDING SITE1 and FGF18 BINDING SITE2, designated SEQ ID:27382 and SEQ ID:9954 respectively, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34934] Another function of VGAM925 is therefore inhibition of Fibroblast Growth Factor 18 (FGF18, Accession NM\_033649), a gene which stimulates hepatic and intestinal proliferation. Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FGF18. The function of

FGF18 has been established by previous studies. The fibroblast growth factors (FGFs; e.g., FGF2; 134920) are a family of growth factors and oncogenes that contain a conserved, approximately 120-amino acid core. Individual FGFs play important roles in embryonic development, cell growth, morphogenesis, tissue repair, inflammation, angiogenesis, and tumor growth and invasion. Ohbayashi et al. (1998) isolated human, mouse, and rat cDNAs encoding a novel member of the FGF family, FGF18. The deduced 207-amino acid human and rat FGF18 proteins are 99% identical. FGF18 contains a typical hydrophobic signal sequence at its N terminus, and the authors demonstrated that recombinant rat Fgf18 can be efficiently secreted by High Five insect cells. Recombinant rat Fgf18 induced neurite outgrowth in PC12 cells. Northern blot analysis of rat adult tissues showed abundant expression of Fgf18 in lung but did not detect Fgf18 expression in other tissues. In rat 14.5- and 19.5-day embryos, in situ hybridization showed Fgf18 expression in several discrete regions. Independently, Hu et al. (1998) isolated human and mouse FGF18 cDNAs. Among known FGF family members, the FGF18 protein is most similar to FGF8 (OMIM Ref. No. 600483) and FGF17 (OMIM Ref. No. 603725), with human

FGF18 showing 60% and 58% identity with human FGF8 and FGF17, respectively. The authors demonstrated that recombinant mouse Fgf18 is glycosylated and can stimulate proliferation of NIH 3T3 cells in vitro in a heparan sulfate-dependent manner. Northern blot analysis of mouse adult tissues showed highest Fgf18 expression in the lung and kidney, and in situ hybridization of mouse 15.5-day embryos detected Fgf18 transcripts primarily in the lung. However, injection of recombinant mouse Fgf18 into normal mice induced proliferation in a wide variety of tissues, with the liver and small intestine appearing to be the primary targets. Hu et al. (1998) showed that transgenic mice overexpressing Fgf18 in the liver exhibited an increase in liver weight and hepatocellular proliferation. By radiation hybrid analysis and FISH, Whitmore et al. (2000) mapped the FGF18 gene to chromosome 5q34.

[34935] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34936] Ohbayashi, N.; Hoshikawa, M.; Kimura, S.; Yamasaki, M.; Fukui, S.; Itoh, N. : Structure and expression of the mRNA encoding a novel fibroblast growth factor, FGF-18. J. Biol. Chem. 273: 18161-18164, 1998. ; and

[34937] Whitmore, T. E.; Maurer, M. F.; Sexson, S.; Raymond, F.; Conklin, D.; Deisher, T. A. : Assignment of fibroblast growth factor 18 (FGF18) to human chromosome 5q34 by use of radiation hyb.

[34938] Further studies establishing the function and utilities of FGF18 are found in John Hopkins OMIM database record ID 603726, and in cited publications numbered 536 and 5836 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Lunatic Fringe Homolog (Drosophila) (LFNG, Accession XM\_166539) is another VGAM925 host target gene. LFNG BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LFNG, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LFNG BINDING SITE, designated SEQ ID:44508, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34939] Another function of VGAM925 is therefore inhibition of Lunatic Fringe Homolog (Drosophila) (LFNG, Accession XM\_166539). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clini-

cal conditions associated with LFNG. Leukocyte Immunoglobulin-like Receptor, Subfamily A (with TM domain), Member 1 (LILRA1, Accession NM\_006863) is another VGAM925 host target gene. LILRA1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LILRA1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LILRA1 BINDING SITE, designated SEQ ID:13736, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34940] Another function of VGAM925 is therefore inhibition of Leukocyte Immunoglobulin-like Receptor, Subfamily A (with TM domain), Member 1 (LILRA1, Accession NM\_006863). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LILRA1. Leukocyte Immunoglobulin-like Receptor, Subfamily B (with TM and ITIM domains), Member 2 (LILRB2, Accession NM\_005874) is another VGAM925 host target gene. LILRB2 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LILRB2, corre-

sponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LILRB2 BINDING SITE, designated SEQ ID:12492, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34941] Another function of VGAM925 is therefore inhibition of Leukocyte Immunoglobulin-like Receptor, Subfamily B (with TM and ITIM domains), Member 2 (LILRB2, Accession NM\_005874). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LILRB2. Synapsin III (SYN3, Accession NM\_133632) is another VGAM925 host target gene. SYN3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SYN3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SYN3 BINDING SITE, designated SEQ ID:28591, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34942] Another function of VGAM925 is therefore inhibition of Synapsin III (SYN3, Accession NM\_133632), a gene which

may be involved in the regulation of neurotransmitter release and synaptogenesis. Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SYN3. The function of SYN3 has been established by previous studies. Synapsins are a family of neuron-specific synaptic vesicle-associated phosphoproteins that have been implicated in synaptogenesis and in the modulation of neurotransmitter release. In mammals, distinct genes for synapsins I (SYN1; 313440) and II (SYN2; 600755) have been identified, each of which encodes 2 alternatively spliced isoforms. Kao et al. (1998) cloned and characterized a third member of the synapsin gene family, synapsin III, from human DNA. Synapsin III gives rise to at least 1 protein isoform, designated synapsin IIIa, in several mammalian species. Synapsin IIIa is associated with synaptic vesicles, and its expression appears to be neuron-specific. The primary structure of synapsin IIIa conforms to the domain model previously described for the synapsin family, with domains A, C, and E exhibiting the highest degree of conservation. Synapsin IIIa contains a novel domain, termed domain J, located between domains C and E. The similarities among synapsins I, II, and III in domain

organization, neuron-specific expression, and subcellular localization suggested a possible role for synapsin III in the regulation of neurotransmitter release and synaptogenesis. Hosaka and Sudhof (1998) identified the human SYN3 gene. Among the rat tissues tested, they found that Syn3 was expressed only in brain. As in other synapsins, the C domain of Syn3 bound ATP with high affinity and ADP with a lower affinity, consistent with a cycle of ATP binding and hydrolysis. However, unlike with Syn1 and Syn2, calcium inhibited ATP binding to Syn3. The authors concluded that calcium has distinct regulatory effects on Syn1, Syn2, and Syn3.

[34943] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[34944] Hosaka, M.; Sudhof, T. C. : Synapsin III, a novel synapsin with an unusual regulation by  $\text{Ca}^{2+}$ . J. Biol. Chem. 273: 13371–13374, 1998. ; and

[34945] Kao, H.-T.; Porton, B.; Czernik, A. J.; Feng, J.; Yiu, G.; Har-  
ing, M.; Benfenati, F.; Greengard, P. : A third member of  
the synapsin gene family. Proc. Nat. Acad. Sci. 95:  
4667–4672, 19.

[34946] Further studies establishing the function and utilities of



SYN3 are found in John Hopkins OMIM database record ID 602705, and in cited publications numbered 1048–1051 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. CLIPR–59 (Accession NM\_015526) is another VGAM925 host target gene. CLIPR–59 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by CLIPR–59, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of CLIPR–59 BINDING SITE, designated SEQ ID:17785, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34947] Another function of VGAM925 is therefore inhibition of CLIPR–59 (Accession NM\_015526). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with CLIPR–59. FLJ22160 (Accession NM\_024585) is another VGAM925 host target gene. FLJ22160 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by FLJ22160, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FLJ22160 BINDING SITE, designated SEQ ID:23819, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34948] Another function of VGAM925 is therefore inhibition of FLJ22160 (Accession NM\_024585). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FLJ22160. HGC6.1.1 (Accession NM\_014354) is another VGAM925 host target gene. HGC6.1.1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by HGC6.1.1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of HGC6.1.1 BINDING SITE, designated SEQ ID:15686, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34949] Another function of VGAM925 is therefore inhibition of HGC6.1.1 (Accession NM\_014354). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HGC6.1.1.

KIAA0514 (Accession NM\_014696) is another VGAM925 host target gene. KIAA0514 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA0514, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA0514 BINDING SITE, designated SEQ ID:16211, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34950] Another function of VGAM925 is therefore inhibition of KIAA0514 (Accession NM\_014696). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA0514. KIAA1089 (Accession XM\_044148) is another VGAM925 host target gene. KIAA1089 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1089, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1089 BINDING SITE, designated SEQ ID:34141, to the nucleotide sequence of VGAM925 RNA, herein designated

VGAM RNA, also designated SEQ ID:3636.

[34951] Another function of VGAM925 is therefore inhibition of KIAA1089 (Accession XM\_044148). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1089. KIAA1110 (Accession XM\_029973) is another VGAM925 host target gene. KIAA1110 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1110, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1110 BINDING SITE, designated SEQ ID:30983, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34952] Another function of VGAM925 is therefore inhibition of KIAA1110 (Accession XM\_029973). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1110. KIAA1274 (Accession XM\_166125) is another VGAM925 host target gene. KIAA1274 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1274, corresponding to

a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1274 BINDING SITE, designated SEQ ID:43908, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34953] Another function of VGAM925 is therefore inhibition of KIAA1274 (Accession XM\_166125). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1274. KIAA1388 (Accession XM\_168030) is another VGAM925 host target gene. KIAA1388 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by KIAA1388, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1388 BINDING SITE, designated SEQ ID:44949, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34954] Another function of VGAM925 is therefore inhibition of KIAA1388 (Accession XM\_168030). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment

of diseases and clinical conditions associated with KIAA1388. KIAA1533 (Accession XM\_057385) is another VGAM925 host target gene. KIAA1533 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by KIAA1533, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of KIAA1533 BINDING SITE, designated SEQ ID:36510, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34955] Another function of VGAM925 is therefore inhibition of KIAA1533 (Accession XM\_057385). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with KIAA1533. PTK6 Protein Tyrosine Kinase 6 (PTK6, Accession NM\_005975) is another VGAM925 host target gene. PTK6 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by PTK6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PTK6 BINDING SITE, designated SEQ ID:12598,

to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34956] Another function of VGAM925 is therefore inhibition of PTK6 Protein Tyrosine Kinase 6 (PTK6, Accession NM\_005975). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PTK6. Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654) is another VGAM925 host target gene. SDC3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by SDC3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SDC3 BINDING SITE, designated SEQ ID:16081, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34957] Another function of VGAM925 is therefore inhibition of Syndecan 3 (N-syndecan) (SDC3, Accession NM\_014654). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SDC3. Spindlin (SPIN, Accession XM\_005421) is another VGAM925 host target gene. SPIN

BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SPIN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPIN BINDING SITE, designated SEQ ID:29979, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34958] Another function of VGAM925 is therefore inhibition of Spindlin (SPIN, Accession XM\_005421). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPIN. Serine Protease Inhibitor, Kunitz Type 1 (SPINT1, Accession XM\_031510) is another VGAM925 host target gene. SPINT1 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by SPINT1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SPINT1 BINDING SITE, designated SEQ ID:31391, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.



[34959] Another function of VGAM925 is therefore inhibition of Serine Protease Inhibitor, Kunitz Type 1 (SPINT1, Accession XM\_031510). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SPINT1. Upstream Binding Protein 1 (LBP-1a) (UBP1, Accession NM\_014517) is another VGAM925 host target gene. UBP1 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by UBP1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of UBP1 BINDING SITE, designated SEQ ID:15845, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34960] Another function of VGAM925 is therefore inhibition of Upstream Binding Protein 1 (LBP-1a) (UBP1, Accession NM\_014517). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with UBP1. ZFP106 (Accession NM\_022473) is another VGAM925 host target gene. ZFP106 BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by

ZFP106, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ZFP106 BINDING SITE, designated SEQ ID:22834, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34961] Another function of VGAM925 is therefore inhibition of ZFP106 (Accession NM\_022473). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ZFP106. LOC147180 (Accession XM\_097207) is another VGAM925 host target gene. LOC147180 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC147180, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC147180 BINDING SITE, designated SEQ ID:40817, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34962] Another function of VGAM925 is therefore inhibition of LOC147180 (Accession XM\_097207). Accordingly, utilities

of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC147180. LOC167040 (Accession XM\_106497) is another VGAM925 host target gene. LOC167040 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC167040, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC167040 BINDING SITE, designated SEQ ID:42200, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34963] Another function of VGAM925 is therefore inhibition of LOC167040 (Accession XM\_106497). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC167040. LOC200213 (Accession XM\_114156) is another VGAM925 host target gene. LOC200213 BINDING SITE is HOST TARGET binding site found in the 5` untranslated region of mRNA encoded by LOC200213, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences

of LOC200213 BINDING SITE, designated SEQ ID:42739, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34964] Another function of VGAM925 is therefore inhibition of LOC200213 (Accession XM\_114156). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC200213. LOC90170 (Accession XM\_029589) is another VGAM925 host target gene. LOC90170 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC90170, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC90170 BINDING SITE, designated SEQ ID:30907, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34965] Another function of VGAM925 is therefore inhibition of LOC90170 (Accession XM\_029589). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC90170. LOC93624 (Accession XM\_052624) is another VGAM925 host target gene. LOC93624 BINDING SITE is

HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC93624, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC93624 BINDING SITE, designated SEQ ID:36014, to the nucleotide sequence of VGAM925 RNA, herein designated VGAM RNA, also designated SEQ ID:3636.

[34966] Another function of VGAM925 is therefore inhibition of LOC93624 (Accession XM\_052624). Accordingly, utilities of VGAM925 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC93624. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 926 (VGAM926) viral gene, which modulates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34967] VGAM926 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM926 was detected is described hereinabove with reference to Figs. 1-8.

[34968] VGAM926 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Infectious Spleen and Kidney Necrosis Virus. VGAM926 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34969] VGAM926 gene encodes a VGAM926 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM926 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM926 precursor RNA is designated SEQ ID:912, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:912 is located at position 67259 relative to the genome of Infectious Spleen and Kidney Necrosis Virus.

[34970] VGAM926 precursor RNA folds onto itself, forming VGAM926 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nu-

cleotide sequence of the second half thereof.

[34971] An enzyme complex designated DICER COMPLEX, `dices` the VGAM926 folded precursor RNA into VGAM926 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 75%) nucleotide sequence of VGAM926 RNA is designated SEQ ID:3637, and is provided hereinbelow with reference to the sequence listing part.

[34972] VGAM926 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM926 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM926 host target RNA comprises three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34973] VGAM926 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM926 host target

RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM926 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM926 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM926 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3' UTR region, this is meant as an example only – these host target binding sites may be located in the 3' UTR region, the 5' UTR region, or in both 3' UTR and 5' UTR regions.

[34974] The complementary binding of VGAM926 RNA, herein designated VGAM RNA, to host target binding sites on VGAM926 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and



BINDING SITE III, inhibits translation of VGAM926 host target RNA into VGAM926 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34975] It is appreciated that VGAM926 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM926 host target genes. The mRNA of each one of this plurality of VGAM926 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM926 RNA, herein designated VGAM RNA, and which when bound by VGAM926 RNA causes inhibition of translation of respective one or more VGAM926 host target proteins.

[34976] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with specific reference to translational inhibition exerted by VGAM926 gene, herein designated VGAM GENE, on one or more VGAM926 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated

only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34977] It is yet further appreciated that a function of VGAM926 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM926 include diagnosis, prevention and treatment of viral infection by Infectious Spleen and Kidney Necrosis Virus. Specific functions, and accordingly utilities, of VGAM926 correlate with, and may be deduced from, the identity of the host target genes which VGAM926 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34978] Nucleotide sequences of the VGAM926 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM926 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM926 folded precursor RNA, herein designated

VGAM FOLDED PRECURSOR RNA, of VGAM926 are further described hereinbelow with reference to Table 1.

[34979] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM926 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM926 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34980] As mentioned hereinabove with reference to Fig. 1, a function of VGAM926 gene, herein designated VGAM is inhibition of expression of VGAM926 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM926 correlate with, and may be deduced from, the identity of the target genes which VGAM926 binds and inhibits, and the function of these target genes, as elaborated hereinbelow.

[34981] Keratocan (KERA, Accession NM\_007035) is a VGAM926 host target gene. KERA BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by KERA, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the

nucleotide sequences of KERA BINDING SITE, designated SEQ ID:13907, to the nucleotide sequence of VGAM926 RNA, herein designated VGAM RNA, also designated SEQ ID:3637.

[34982] A function of VGAM926 is therefore inhibition of Kerato-  
can (KERA, Accession NM\_007035), a gene which may be  
important in developing and maintaining corneal trans-  
parency and for the structure of the stromal matrix. Ac-  
cordingly, utilities of VGAM926 include diagnosis, preven-  
tion and treatment of diseases and clinical conditions as-  
sociated with KERA. The function of KERA and its associa-  
tion with various diseases and clinical conditions, has  
been established by previous studies, as described here-  
inabove with reference to VGAM723.HT008 (Accession  
XM\_008246) is another VGAM926 host target gene.  
HT008 BINDING SITE is HOST TARGET binding site found  
in the 3' untranslated region of mRNA encoded by  
HT008, corresponding to a HOST TARGET binding site  
such as BINDING SITE I, BINDING SITE II or BINDING SITE III.  
Table 2 illustrates the complementarity of the nucleotide  
sequences of HT008 BINDING SITE, designated SEQ  
ID:30073, to the nucleotide sequence of VGAM926 RNA,  
herein designated VGAM RNA, also designated SEQ

ID:3637.

[34983] Another function of VGAM926 is therefore inhibition of HT008 (Accession XM\_008246). Accordingly, utilities of VGAM926 include diagnosis, prevention and treatment of diseases and clinical conditions associated with HT008. LOC151827 (Accession XM\_087317) is another VGAM926 host target gene. LOC151827 BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by LOC151827, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LOC151827 BINDING SITE, designated SEQ ID:39168, to the nucleotide sequence of VGAM926 RNA, herein designated VGAM RNA, also designated SEQ ID:3637.

[34984] Another function of VGAM926 is therefore inhibition of LOC151827 (Accession XM\_087317). Accordingly, utilities of VGAM926 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LOC151827. Fig. 1 further provides a conceptual description of a novel bioinformatically detected viral gene of the present invention, referred to here as Viral Genomic Address Messenger 927 (VGAM927) viral gene, which modu-

lates expression of respective host target genes thereof, the function and utility of which host target genes is known in the art.

[34985] VGAM927 is a novel bioinformatically detected regulatory, non protein coding, viral micro RNA (miRNA) gene. The method by which VGAM927 was detected is described hereinabove with reference to Figs. 1–8.

[34986] VGAM927 gene, herein designated VGAM GENE, is a viral gene contained in the genome of Infectious Spleen and Kidney Necrosis Virus. VGAM927 host target gene, herein designated VGAM HOST TARGET GENE, is a human gene contained in the human genome.

[34987] VGAM927 gene encodes a VGAM927 precursor RNA, herein designated VGAM PRECURSOR RNA. Similar to other miRNA genes, and unlike most ordinary genes, VGAM927 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of VGAM927 precursor RNA is designated SEQ ID:913, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:913 is located at position 65593 relative to the genome of Infectious Spleen and Kidney Necrosis Virus.

[34988] VGAM927 precursor RNA folds onto itself, forming

VGAM927 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, which has a two-dimensional `hairpin structure`. As is well known in the art, this `hairpin structure`, is typical of RNA encoded by miRNA genes, and is due to the fact that the nucleotide sequence of the first half of the RNA encoded by a miRNA gene is an accurate or partial inversed-reversed sequence of the nucleotide sequence of the second half thereof.

[34989] An enzyme complex designated DICER COMPLEX, `dices` the VGAM927 folded precursor RNA into VGAM927 RNA, herein designated VGAM RNA, a single stranded ~22 nt long RNA segment. As is known in the art, `dicing` of a hairpin structured RNA precursor product into a short ~22nt RNA segment is catalyzed by an enzyme complex comprising an enzyme called Dicer together with other necessary proteins. A probable (over 67%) nucleotide sequence of VGAM927 RNA is designated SEQ ID:3638, and is provided hereinbelow with reference to the sequence listing part.

[34990] VGAM927 host target gene, herein designated VGAM HOST TARGET GENE, encodes a corresponding messenger RNA, VGAM927 host target RNA, herein designated VGAM HOST TARGET RNA. VGAM927 host target RNA comprises

three regions, as is typical of mRNA of a protein coding gene: a 5` untranslated region, a protein coding region and a 3` untranslated region, designated 5`UTR, PROTEIN CODING and 3`UTR respectively.

[34991] VGAM927 RNA, herein designated VGAM RNA, binds complementarily to one or more host target binding sites located in untranslated regions of VGAM927 host target RNA, herein designated VGAM HOST TARGET RNA. This complementary binding is due to the fact that the nucleotide sequence of VGAM927 RNA is an accurate or a partial inversed-reversed sequence of the nucleotide sequence of each of the host target binding sites. As an illustration, Fig. 1 shows three such host target binding sites, designated BINDING SITE I, BINDING SITE II and BINDING SITE III respectively. It is appreciated that the number of host target binding sites shown in Fig. 1 is meant as an illustration only, and is not meant to be limiting – VGAM927 RNA, herein designated VGAM RNA, may have a different number of host target binding sites in untranslated regions of a VGAM927 host target RNA, herein designated VGAM HOST TARGET RNA. It is further appreciated that while Fig. 1 depicts host target binding sites in the 3`UTR region, this is meant as an example



only – these host target binding sites may be located in the 3`UTR region, the 5`UTR region, or in both 3`UTR and 5`UTR regions.

[34992] The complementary binding of VGAM927 RNA, herein designated VGAM RNA, to host target binding sites on VGAM927 host target RNA, herein designated VGAM HOST TARGET RNA, such as BINDING SITE I, BINDING SITE II and BINDING SITE III, inhibits translation of VGAM927 host target RNA into VGAM927 host target protein, herein designated VGAM HOST TARGET PROTEIN. VGAM host target protein is therefore outlined by a broken line.

[34993] It is appreciated that VGAM927 host target gene, herein designated VGAM HOST TARGET GENE, in fact represents a plurality of VGAM927 host target genes. The mRNA of each one of this plurality of VGAM927 host target genes comprises one or more host target binding sites, each having a nucleotide sequence which is at least partly complementary to VGAM927 RNA, herein designated VGAM RNA, and which when bound by VGAM927 RNA causes inhibition of translation of respective one or more VGAM927 host target proteins.

[34994] It is further appreciated by one skilled in the art that the mode of translational inhibition illustrated by Fig. 1 with

specific reference to translational inhibition exerted by VGAM927 gene, herein designated VGAM GENE, on one or more VGAM927 host target gene, herein designated VGAM HOST TARGET GENE, is in fact common to other known non-viral miRNA genes. As mentioned hereinabove with reference to the background section, although a specific complementary binding site has been demonstrated only for some of the known miRNA genes (primarily Lin-4 and Let-7), all other recently discovered miRNA genes are also believed by those skilled in the art to modulate expression of other genes by complementary binding, although specific complementary binding sites of these other miRNA genes have not yet been found (Ruvkun G., `Perspective: Glimpses of a tiny RNA world`, Science 294,779 (2001)).

[34995] It is yet further appreciated that a function of VGAM927 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of viral infection by Infectious Spleen and Kidney Necrosis Virus. Specific functions, and accordingly utilities, of VGAM927 correlate with, and may be deduced from, the identity of the host target genes which

VGAM927 binds and inhibits, and the function of these host target genes, as elaborated hereinbelow.

[34996] Nucleotide sequences of the VGAM927 precursor RNA, herein designated VGAM PRECURSOR RNA, and of the `diced` VGAM927 RNA, herein designated VGAM RNA, and a schematic representation of the secondary folding of VGAM927 folded precursor RNA, herein designated VGAM FOLDED PRECURSOR RNA, of VGAM927 are further described hereinbelow with reference to Table 1.

[34997] Nucleotide sequences of host target binding sites, such as BINDING SITE-I, BINDING SITE-II and BINDING SITE-III of Fig. 1, found on VGAM927 host target RNA, and schematic representation of the complementarity of each of these host target binding sites to VGAM927 RNA, herein designated VGAM RNA, are described hereinbelow with reference to Table 2.

[34998] As mentioned hereinabove with reference to Fig. 1, a function of VGAM927 gene, herein designated VGAM is inhibition of expression of VGAM927 target genes. It is appreciated that specific functions, and accordingly utilities, of VGAM927 correlate with, and may be deduced from, the identity of the target genes which VGAM927 binds and inhibits, and the function of these target genes,

as elaborated hereinbelow.

[34999] Adrenergic, Beta-3-, Receptor (ADRB3, Accession NM\_000025) is a VGAM927 host target gene. ADRB3 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ADRB3, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ADRB3 BINDING SITE, designated SEQ ID:5461, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35000] A function of VGAM927 is therefore inhibition of Adrenergic, Beta-3-, Receptor (ADRB3, Accession NM\_000025), a gene which stimulates adenylyl cyclase activity and regulates lipolysis. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ADRB3. The function of ADRB3 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM179. Ankyrin-like with Transmembrane Domains 1 (ANKTM1, Accession NM\_007332) is another VGAM927 host target gene. ANKTM1 BINDING SITE is HOST TARGET

binding site found in the 3' untranslated region of mRNA encoded by ANKTM1, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ANKTM1 BINDING SITE, designated SEQ ID:14259, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35001] Another function of VGAM927 is therefore inhibition of Ankyrin-like with Transmembrane Domains 1 (ANKTM1, Accession NM\_007332), a gene which attaches integral membrane proteins to cytoskeletal elements. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ANKTM1. The function of ANKTM1 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM644. Rho GTPase Activating Protein 6 (ARHGAP6, Accession NM\_001174) is another VGAM927 host target gene. ARHGAP6 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ARHGAP6, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or

BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ARHGAP6 BINDING SITE, designated SEQ ID:6840, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35002] Another function of VGAM927 is therefore inhibition of Rho GTPase Activating Protein 6 (ARHGAP6, Accession NM\_001174), a gene which activates the rho-type GTPases by converting them to an inactive GTP-bound state. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ARHGAP6. The function of ARHGAP6 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM55. Attractin (ATRN, Accession NM\_139321) is another VGAM927 host target gene. ATRN BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by ATRN, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of ATRN BINDING SITE, designated SEQ ID:29296, to the nucleotide sequence of VGAM927 RNA,

herein designated VGAM RNA, also designated SEQ ID:3638.

[35003] Another function of VGAM927 is therefore inhibition of Attractin (ATRN, Accession NM\_139321), a gene which is involved in the initial immune cell clustering during inflammatory response. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with ATRN. The function of ATRN and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM53.B-cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898) is another VGAM927 host target gene. BCL11B BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by BCL11B, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of BCL11B BINDING SITE, designated SEQ ID:23158, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35004] Another function of VGAM927 is therefore inhibition of B-

cell CLL/lymphoma 11B (zinc finger protein) (BCL11B, Accession NM\_022898). Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with BCL11B. Fibroblast Activation Protein, Alpha (FAP, Accession NM\_004460) is another VGAM927 host target gene. FAP BINDING SITE is HOST TARGET binding site found in the 5' untranslated region of mRNA encoded by FAP, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of FAP BINDING SITE, designated SEQ ID:10766, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35005] Another function of VGAM927 is therefore inhibition of Fibroblast Activation Protein, Alpha (FAP, Accession NM\_004460), a gene which may have a role in tissue remodeling during development and wound healing. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with FAP. The function of FAP has been established by previous studies. Fibroblast activation protein-alpha (FAP-alpha) is an inducible cell surface glycoprotein



that was originally identified in cultured fibroblasts using monoclonal antibody F19. Immunohistochemical studies have shown that FAP- $\alpha$  is transiently expressed in certain normal fetal mesenchymal tissues but that normal adult tissues as well as malignant epithelial, neural, and hematopoietic cells are generally FAP- $\alpha$ -negative. However, most of the common types of epithelial cancers contain abundant FAP- $\alpha$ -reactive stromal fibroblasts. Scanlan et al. (1994) cloned an FAP- $\alpha$  cDNA from a WI-38 human fibroblast cDNA expression library by immunoselection using antibody F19. The predicted 760-amino acid FAP- $\alpha$  protein (GenBank 1888316) is a type II integral membrane protein with a large C-terminal extracellular domain, which contains 6 potential N-glycosylation sites, 13 cysteine residues, and 3 segments that correspond to highly conserved catalytic domains of serine proteases; a hydrophobic transmembrane segment; and a short cytoplasmic tail. FAP- $\alpha$  shows 48% amino acid identity with dipeptidyl peptidase IV (DPP4; 102720) and 30% identity with DPP4-related protein (DPPX; 126141). Northern blot analysis detected a 2.8-kb FAP- $\alpha$  mRNA in fibroblasts. Seprase is a 170-kD integral membrane gelatinase whose expression

correlates with the invasiveness of human melanoma and carcinoma cells. Goldstein et al. (1997) cloned and characterized a seprase cDNA. They suggested that seprase and FAP-alpha are the same protein and products of the same gene. Pineiro-Sanchez et al. (1997) isolated seprase protein from the cell membranes and shed vesicles of human melanoma LOX cells. Serine protease inhibitors blocked the gelatinase activity of seprase, suggesting that seprase contains a catalytically active serine residue(s). The authors found that seprase is composed of monomeric, N-glycosylated 97-kD subunits that are proteolytically inactive. They concluded that seprase is similar to DPP4 in that their proteolytic activities are dependent upon subunit association.

[35006] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[35007] Pineiro-Sanchez, M. L.; Goldstein, L. A.; Dodt, J.; Howard, L.; Yeh, Y.; Tran, H.; Argraves, W. S.; Chen, W.-T. : Identification of the 170-kDa melanoma membrane-bound gelatinase (seprase) as a serine integral membrane protease. J. Biol. Chem. 272: 7595-7601, 1997. ; and

[35008] Scanlan, M. J.; Raj, B. K. M.; Calvo, B.; Garin-Chesa, P.;

Sanz-Moncasi, M. P.; Healey, J. H.; Old, L. J.; Rettig, W. J. : Molecular cloning of fibroblast activation protein alpha, a me.

[35009] Further studies establishing the function and utilities of FAP are found in John Hopkins OMIM database record ID 600403, and in cited publications numbered 7113–7116 listed in the bibliography section hereinbelow, which are also hereby incorporated by reference. Leukemia Inhibitory Factor (cholinergic differentiation factor) (LIF, Accession NM\_002309) is another VGAM927 host target gene. LIF BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by LIF, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of LIF BINDING SITE, designated SEQ ID:8097, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35010] Another function of VGAM927 is therefore inhibition of Leukemia Inhibitory Factor (cholinergic differentiation factor) (LIF, Accession NM\_002309). Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with LIF. Phos-

phosphoribosyl Pyrophosphate Synthetase 2 (PRPS2, Accession NM\_002765) is another VGAM927 host target gene. PRPS2 BINDING SITE is HOST TARGET binding site found in the 3' untranslated region of mRNA encoded by PRPS2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of PRPS2 BINDING SITE, designated SEQ ID:8655, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35011] Another function of VGAM927 is therefore inhibition of Phosphoribosyl Pyrophosphate Synthetase 2 (PRPS2, Accession NM\_002765), a gene which generates the PRPP needed for initiation of purine biosynthesis. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with PRPS2. The function of PRPS2 and its association with various diseases and clinical conditions, has been established by previous studies, as described hereinabove with reference to VGAM828. Solute Carrier Family 10 (sodium/bile acid cotransporter family), Member 2 (SLC10A2, Accession NM\_000452) is another VGAM927 host target gene. SLC10A2 BINDING SITE is HOST TARGET

binding site found in the 3` untranslated region of mRNA encoded by SLC10A2, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of SLC10A2 BINDING SITE, designated SEQ ID:6064, to the nucleotide sequence of VGAM927 RNA, herein designated VGAM RNA, also designated SEQ ID:3638.

[35012] Another function of VGAM927 is therefore inhibition of Solute Carrier Family 10 (sodium/bile acid cotransporter family), Member 2 (SLC10A2, Accession NM\_000452). Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with SLC10A2. Signal Transducing Adaptor Molecule (SH3 domain and ITAM motif) 1 (STAM, Accession NM\_003473) is another VGAM927 host target gene. STAM BINDING SITE is HOST TARGET binding site found in the 3` untranslated region of mRNA encoded by STAM, corresponding to a HOST TARGET binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 2 illustrates the complementarity of the nucleotide sequences of STAM BINDING SITE, designated SEQ ID:9539, to the nucleotide sequence of VGAM927 RNA, herein des-

ignated VGAM RNA, also designated SEQ ID:3638.

[35013] Another function of VGAM927 is therefore inhibition of Signal Transducing Adaptor Molecule (SH3 domain and ITAM motif) 1 (STAM, Accession NM\_003473), a gene which is as an adaptor molecule involved in the downstream signaling of cytokine receptors. Accordingly, utilities of VGAM927 include diagnosis, prevention and treatment of diseases and clinical conditions associated with STAM. The function of STAM has been established by previous studies. Stimulation of cells with cytokines results in a signal transduction cascade involving cytokine receptors, Janus kinases (JAKs) and signal transducers and activators of transcription (STATs). In order to investigate signal transduction downstream of JAK3 (OMIM Ref. No. 600173), Takeshita et al. (1996) screened for molecules induced after stimulation of cells with the cytokine IL2 (OMIM Ref. No. 147680). Their screen identified a novel molecule, which they named STAM for 'signal-transducing adaptor molecule.' They cloned the human STAM cDNA from a T-cell cDNA library and found that it encodes a 540-amino acid polypeptide. The approximately 70-kD protein product was precipitated by anti-phosphotyrosine. Northern blot analysis indicated that STAM was expressed

as a 2.9-kb message in all tissue and cell types examined. The STAM sequence contains a Src-homology 3 (SH3) domain and an immunoreceptor tyrosine-based activation motif (ITAM). Takeshita et al. (1996) suggested that STAM acts as an adaptor molecule in signal transduction pathways from cytokine receptors. Asao et al. (1997) showed that HGS (OMIM Ref. No. 604375) binds to STAM via coiled-coil sequences and appears to regulate proliferation in response to cytokines.

[35014] Full details of the abovementioned studies are described in the following publications, the disclosure of which are hereby incorporated by reference:

[35015] Asao, H.; Sasaki, Y.; Arita, T.; Tanaka, N.; Endo, K.; Kasai, H.; Takeshita, T.; Endo, Y.; Fujita, T.; Sugamura, K. : Hrs is associated with STAM, a signal-transducing adaptor molecule: its suppressive effect on cytokine-induced cell growth. J. Biol. Chem. 272: 32785-32791, 1997. ; and

[35016] Takeshita, T.; Arita, T.; Asao, H.; Tanaka, N.; Higuchi, M.; Kuroda, H.; Kaneko, K.; Munakata, H.; Endo, Y.; Fujita, T.; Sugamura, K. : Cloning of a novel signal-transducing adaptor mol.

[35017] Further studies establishing the function and utilities of STAM are found in John Hopkins OMIM database record ID